aviesan

alliance nationale
pour les sciences de la vie et de la santé

Directory

Institute

Pathophysiology Metabolism & Nutrition

Circulatory system,
Hemostasis,
Pneumology,
Dermatology,
Diabetes,
Metabolism/Nutrition,
Endocrinology
Gastroenterology,
Hepatology,
Uro-Nephrology,
Osteoarticular system

- July 2018 -

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Introduction

1 – Fields covered

The life science Institute *Pathophysiology, Metabolism & Nutrition* (PMN) covers a wide spectrum of research in physiology, experimental medicine and human diseases. The fields covered include heart and vessels, lungs, endocrine organs, liver, kidney, skin, joints and bones, and organs involved in nutrient processing, from all aspects of nutrition, from the control of food intake and nutritional behavior to digestive processing, control of substrate use and storage. The diseases in question frequently show common biological mechanisms and often lack of suitable treatments designed on a pathophysiological basis.

2 – Major scientific challenges in biology and medicine

- **Public health care challenges**

Among diseases within the PMN scope, cardiovascular, respiratory, metabolic and nutritional diseases with their devastating complications represent a major public health care challenge. Diabetes, hyperlipidemia, obesity, renal insufficiency lead to cardiovascular disease, the major cause of mortality in industrialized countries and usually develop in relation with atherosclerosis.

Coronary artery disease, stroke and chronic heart failure are responsible for 75% of cardiovascular-related deaths. They represent 29% of deaths in France, almost equaling deaths due to cancer. Thrombotic diseases are very prevalent, arterial thrombosis (ischaemic diseases) and venous thrombosis (thrombo-embolic disease) are the world's leading cause of death. The prevalence of constitutional haemorrhagic diseases is limited, but their social and economic impact is significant, as in the case of haemophilia.

Respiratory diseases (asthma, chronic obstructive pulmonary disease, COPD; pulmonary fibroses) affect millions of people in France and their incidence is increasing. COPD alone already represents the third-largest cause of death in Europe (sixth in the world).

The prevalence of diabetes is 7.4% in France in the age range 20 to 79 (IDF 2015). The increasing prevalence of diabetes parallels that of obesity, which raised to 15.8% among men and 15.6% among women in France (age range 30 to 69, INVS 2013). Regarding the visceral obesity the prevalence reaches 41.6% and 48.5% respectively. Diabetes is among the leading causes of blindness, end stage renal disease, non-traumatic limb amputation in adults and coronary heart disease. Type 2 diabetes is a multifactorial disease that shows heterogeneity in many respects and is often a manifestation of a much broader underlying disorder often referred to as the metabolic syndrome, an operational paradigm that includes hyperinsulinaemia, dyslipidaemia, hypertension, visceral obesity, hypercoagulability and microalbuminuria. Metabolic syndrome also leads to various non-vascular complications, including steatohepatis, cirrhosis or arthrosis. The metabolic epidemics and its cardiovascular complications although world-wide have been most pronounced in non-European populations, as shown by studies from Native American and Canadian communities, Pacific and Indian Ocean island populations or populations throughout Asia.

Paradoxically, malnutrition is also a major threat to global human health and survival. Recent estimates indicate that nutritional deficiencies account for 3 million child deaths each year in less-developed countries while progress toward designing effective life-saving interventions is currently hampered by serious gaps in our understanding of nutrient metabolism in the human. Denutrition is further observed in 40% of patients suffering from chronic diseases, in 30 to 50% of hospitalized patients of all pathologies and is an independent factor for morbidity/mortality. Overall, there is a need for an increased research effort focusing on nutrition and its disorders, including the interrelationship with the environment, the human microbiome, digestive physiology, nutritional behaviors or food security.

Diseases of the bones and joints are also a concern for the French, particularly due to ageing of the population. On their own they represent half of chronic diseases in people over 65 and are a major cause of invalidity (arthrosis is the second largest handicap factor in men, the fourth in women).

Among the over 50s, one women in four and one man in eight will be affected by osteoporosis during their lives.

Skin diseases include a proportion of allergic complaints (atopic dermatitis, contact eczema, occupational dermatoses, photo-allergies, urticaria and skin accidents due to oral administration of a drug (toxicodermatitis)) and a proportion of chronic inflammatory disorders (psoriasis, atopic dermatitis, pelada, etc.). Among this latter group, psoriasis, affects between two and three million people in France and is associated with a significant change in the quality of life, often leading to a severe social handicap. The impact of this dermatosis on the quality of life is as significant as that caused by asthma, diabetes or chronic cardiac ischaemic diseases. The social cost of psoriasis is therefore considerable. Ageing of the population is increasingly frequently accompanied by chronic vascular complaints of the lower limbs. Their treatment is complex and should be multi-disciplinary, ideally as part of a care network led by dermatologists specialised in the field of cicatrisation.

Other diseases that are in the scope of the Institute are frequent and/or carry high morbidity/mortality rates. Basic and clinical research is required to progress in our understanding of the mechanisms involved in cardiac, vascular, respiratory, renal, endocrine, digestive, dermatologic and osteoarticular disorders.

- **Scientific challenges**

Diseases implicating heart and vessels, lungs, endocrine tissues, kidney, liver, skin, bone and joints and the digestive tract, although organ-specific, cannot be considered independently of the numerous interactions with the whole organism and the environment. Transversal aspects of physiology and pathology will be emphasized within the scope of the PMN Institute. Underlying fundamental research and biological issues that need to be addressed correspondingly cover a large field of disciplines requiring strong links between institutional partners, as well as with industrial partners. All these diseases share: 1- an incomplete knowledge of the genes involved in their etiology, a situation which is rapidly changing thanks in particular to the new genomic approaches, 2- an insufficient basic knowledge of gene and protein functions in target organs as well as their interaction with the environment; 3- incomplete understanding of pathophysiological mechanisms of diseases expressed within corresponding tissues, i.e. of mechanisms of initiation and progression of disease processes; 4- the general insufficiency of available treatments and preventive strategies based on a better understanding of the mechanisms of common diseases; 5- the understudied strategies of cell therapy, which could benefit to many of these diseases; 6- the importance of discovering new biomarkers that would be useful for diagnostic, prognostic and treatment guidance.

1) Gene/protein-function studies in physiology and interactions with environment

The availability of gene sequences encoding for molecules of unknown functions emphasizes the need for extensive gene-function studies and for the characterization of tissue distribution of newly identified genes. As part of this task, the development of new models to empower these studies is required. Other emphasis is required on development biology, on studies of ageing mechanisms, on comparative genomics with the goal of better understanding of human gene and protein functions, on integrative physiology to decipher signalling and metabolic pathways and interactions at the whole organism level, on the understanding of gene interactions and gene networks that impact on individual cell and tissue functions, on epigenetics and metagenomics to study gene interactions with the environment. The sequence of an increasing number of individual human genomes also paves the path toward in depth understanding of human gene and post-transcriptional diversity in cell, tissue and organ physiology. With few exceptions, the miRNA target genes and the mechanism of target suppression are currently unknown because reliable experimental methods for comprehensively identifying the miRNA targets have yet to be developed.

2) Disease-initiating mechanisms and mechanisms of disease progression in common diseases.

Mechanisms that trigger destructive processes within target tissues are seldom identified. Other than certain rare monogenic diseases involving key genes in cell function, common diseases usually develop on a multigenic susceptibility background associating “normal” gene variants, often affecting quantitative traits (intermediate phenotypes) that contribute to the clinical phenotype observed, most often interacting with environmental factors as part of a multifactorial process. As triggering factors remain elusive in most cases, new hypotheses in disease initiation should be tested, possibly stochastic events in initiation process or early external factors within perinatal or prenatal development. Genetic and molecular epidemiology can help to isolate specific risk factors, especially to identify subjects at risk of sudden death, a major problem in industrially developed countries. Furthermore, striking changes in the incidence of major multifactorial diseases will need to be addressed. Delineating initiation and progression events in common diseases is a challenge that applies at three levels: genetic susceptibility, cell pathways involved in disease and the role of environmental factors. Within a given genetic background, some genes concur at initiating the disease process while others control disease progression that directly impact on the age at disease onset following a preclinical phase. Seemingly, some environmental factors trigger the disease process while other modulate disease progression.

3) Treatments based on mechanisms of diseases

In many diseases within the PMN scope, current treatments remain insufficient for different reasons, depending of the field covered. Some treatments remain symptomatic or palliative (e.g. treatments of chronic heart disease, substitutive therapies in endocrine diseases, dialysis in end stage renal diseases, organ transplantation in renal, heart, lung, liver or gut failures). In other examples, pathophysiological treatment that remain non-specific (e.g. immunosuppressive treatments in immune/inflammatory diseases) induces severe side effects. Novel strategies aimed at controlling the immune/inflammatory response should be developed (small molecules targeting inflammatory pathways, monoclonal antibodies vaccination). In a third set of diseases, preventive strategies are available but only target biomarkers that relate with a risk factor associated with the disease process (e.g. treatment of obesity to prevent metabolic and cardiovascular diseases) but in most cases the risk factor that is amenable to treatment is only part of the susceptibility that underlies the pathological process (e.g. atherosclerosis in case of cardiovascular diseases). Finally, major ischemic diseases (heart, brain, limbs, kidney) suffer from the lack of treatments able to protect tissues for ischemic sequelae.

4) Strategies for cell replacement

Among the aforementioned palliative therapeutic strategies, organ transplantation have developed since the mid fifties. They have now been generalized in many field of medicine (e.g. renal transplantation imply a favorable risk to benefit ratio as compared to dialysis, heart or liver transplantation are the only feasible strategies in corresponding organ failures). However, transplantation still face the lack of organ donors, significant side effects relating with long term immunosuppression and the complexity of surgical procedures. Evolution of organ replacement strategies faces the need for new strategies to provide cells or organs amenable to transplantation in human diseases. An underlying emphasis will be in study of organ development and molecular mechanisms involved, the study of stem cell biology and strategies to develop artificial or in vitro-engineered tissues and organs. Embryonic and adult stem cell transplantation as a potential means of regenerating injured tissues is currently receiving a great deal of interest. To exploit this as a viable therapy, methods need to be developed for harvesting and expansion of stem cells in sufficient quantities. This in turn implies greater knowledge of the pathways controlling replication and maturation of stem cells. Genomic and proteomic methods are ideally suited to provide these new

insights. Standardised experimental animal models that reproduce human disease are required for translational research. Furthermore information regarding the safety of cells based therapy in patients is needed.

- **Technological challenges**

To achieve insight into physiology and pathophysiological processes in the fields covered by the PMN institute, technological challenges are multifold. The human genome opens the need for better understanding of gene regulation and interaction with the environment, both in physiology and in pathology. Beyond high-throughput DNA sequencing and transcriptomics, epigenetics and metagenomics will need to be developed to get insight into both organ development and physiology and into mechanisms of common diseases. A parallel challenge is, at the other extreme of the spectrum from fundamental research to applied medicine, the need for setting up clinical phenotyping platforms including sensory platform in an effort towards an improved classification of common diseases that, as aforementioned, lack identified aetiologies on which medical classifications may rely on.

Specific challenges:

1) Development of improved models to apply the advances of genetics, genomics transcriptomics and proteomics to the study of gene and protein functions, and creation of tools (platforms) enabling genomic analysis of epigenetic programs and changes in individual or small groups of cells in integrated contexts

2) Development of appropriate facilities for study of both large animals models and small model organisms where teams of researchers and clinicians can address molecular, physiological and pathological questions by studying underlying mechanisms in integrated contexts. This includes the development of advanced imageing techniques (e.g. cell imageing, high-resolution imageing, multiphoton microscopy, small animal imageing).

3) Development of translational research networks at the crossroad of research institutes and hospitals with the aim of developing biomarkers and innovative therapeutic strategies.

4) Optimize the use of the important human bioresources (blood, plasma, DNA, tissue samples) available and currently being constituted in the fields covered by the PMN Institute, and facilitate their exploitation using advanced technology.

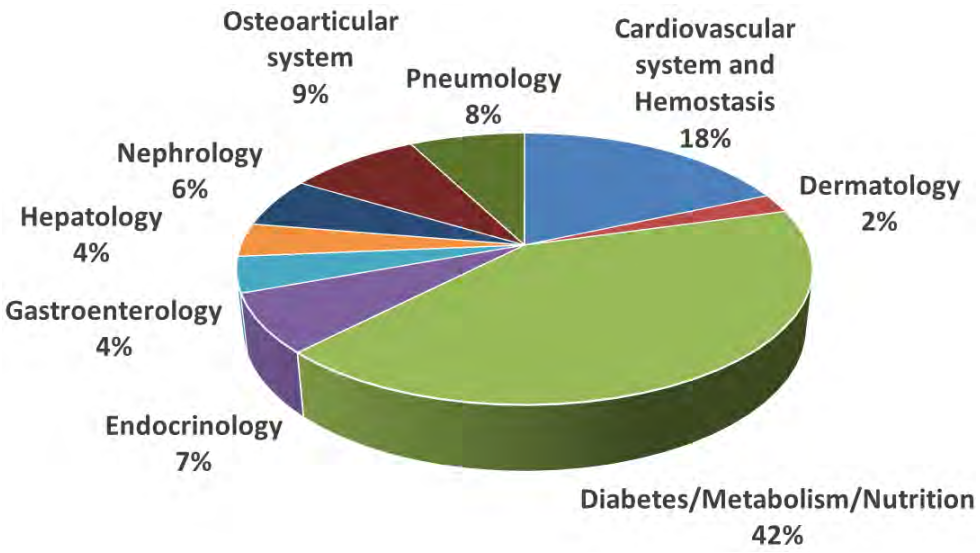
5) Establishment of resource centres centralising interactive data sets such as that (Standards based Infrastructure with Distributed Resources, SIDR) set up by the CNRS/INIST to better collect, annotate, exploit and harness qualitative and quantitative data sets from different sources to be used in modelling and systems biology approaches for understanding basic biological mechanisms and pathophysiological regulations.

3 – ITMO PMN in numbers

- 353 research teams
- 1,500 researchers
- 1,130 hospital practitioners
- 15,800 publications a year

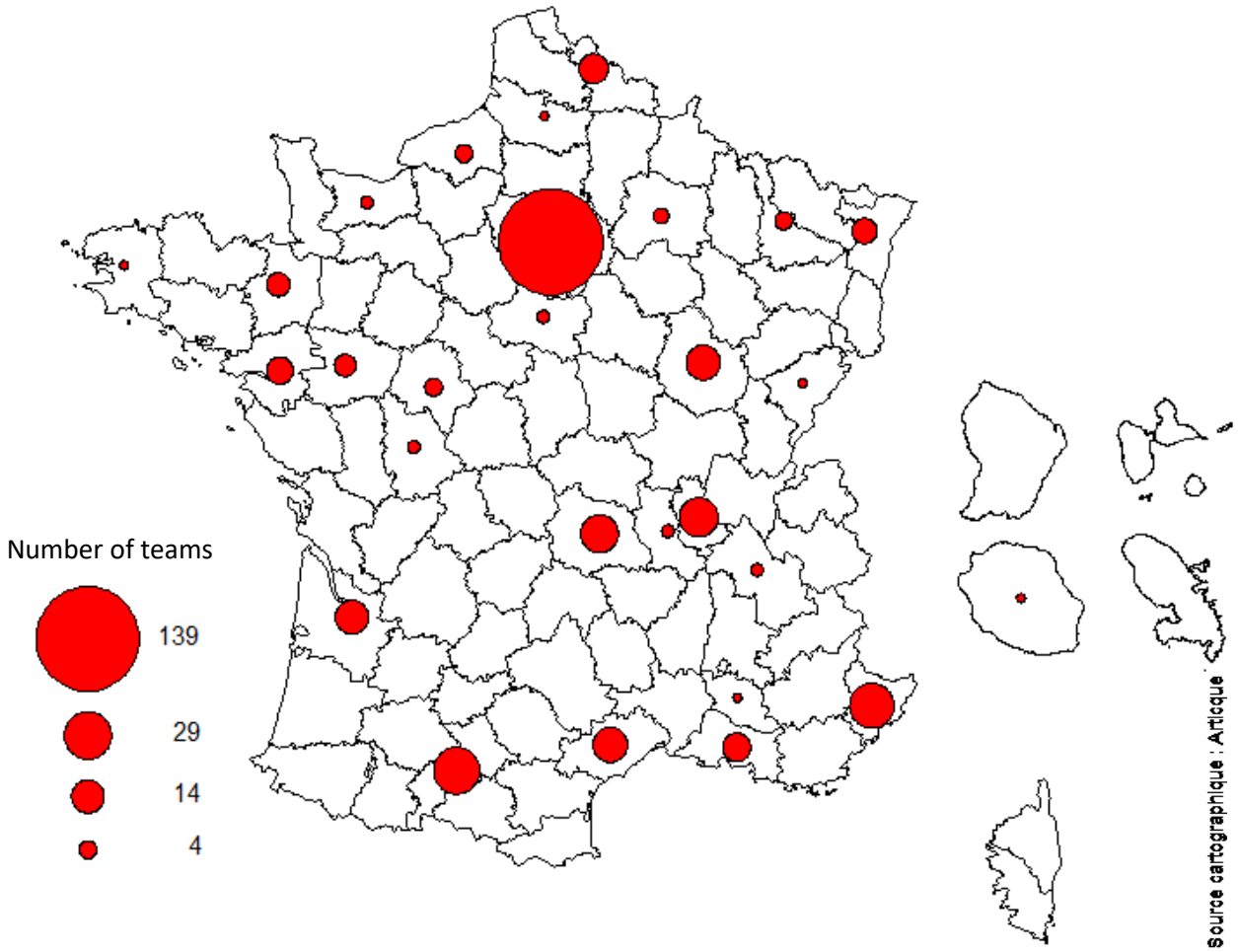
Team distribution by domain

- The teams are distributed in the following domains:



Geographical distribution

- About 39% of ITMO PMN teams are based in the Paris area.
- Teams are affiliated to 34 universities (5 in Paris) and 11 *Grandes Ecoles* (4 in Paris).



- Some spots display focused and specific research activities:
  - metabolism/nutrition in Bordeaux, Clermont-Ferrand, Dijon and Lyon
  - cardiovascular and metabolic diseases in Toulouse
  - diabetes in Lille
  - cardiometabolism in Nantes

- In the Paris area, the teams are spread out on 30 spots. Some of them are focused on specific field:
  - cardiovascular in Georges Pompidou European Hospital
  - cardiometabolism in Pitié Salpêtrière Hospital
  - diabetes in Cochin.
  - metabolism/nutrition in Jouy-en-Josas
  - hepato/gastroenterology in Bichat Hospital

Other research infrastructures

- Clinical Investigation Centres (CIC)

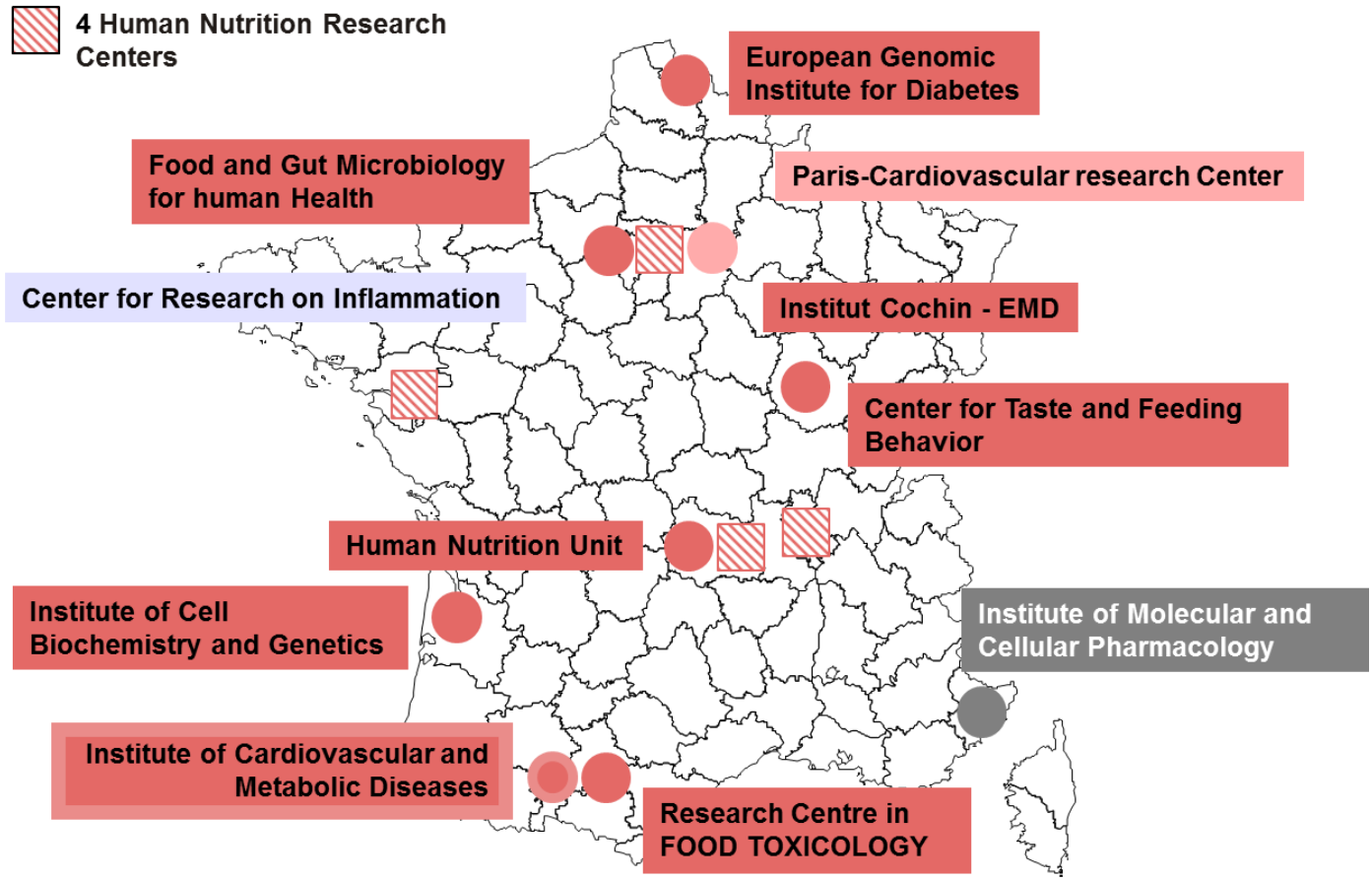
Set up by the Ministry of Health through the DGOS (Department for the supply of healthcare) and Inserm (the National Institute for Health and Medical Research), the CICs are clinical research infrastructures dedicated to the organisation, coordination and realization of physiology, pathophysiology and/or therapy protocols with the aim to increase knowledge of diseases, their prevention and treatments.
The CICs' activities are always closely linked to the University Hospital research programs. Actually there are 54 CICs spread out in France. 26 are connected through 8 national thematic networks, 3 of them displaying the following themes: "Thrombosis", "Cardiovascular diseases" and "Hepatology and Gastroenterology".
More than 40% of protocols developed in CIC networks relate to one of the domains covered by ITMO PMN.

- Networks for excellence in clinical research

The national infrastructure for French clinical research F-CRIN approved networks for excellence in clinical research to lead original and internationally appealing scientific programmes. These programmes have targeted themes with major potential for development and benefit from renowned collective scientific and methodological expertise with a strong capacity for research. Out of the 8 approved Networks, 5 are specialized to the following themes: "Thrombosis", "Obesity", "Cardiovascular diseases", "Chronic kidney diseases" and "Autoimmune and autoinflammatory diseases".

- Human Nutrition Research Centers (HNRC)

The Human Nutrition Research Centers were set up to develop research on clinical nutrition in healthy human and out patients, to provide specific facilities regarding both investigation tools and specific food conditioning. 4 centers were created in Lyon, Clermont-Ferrand, Nantes and Paris (Ile de France). Each of these centers is a combination of several research units from INRA, INSERM, Universities and clinical units from University Hospitals with specific facilities.



French initiative « Investments for the Future»

Launched in 2009 by the French Government, the Investments for the Future programmes are strategic initiatives which aim to boost French competitiveness by investing particularly in research and higher education. This strong financial support to research, higher education and innovation aimed at promoting excellence and the development of high-level projects and clusters and strengthening France's capacity for innovation.
Among others, the main programmes in the fields of the PMN institute are listed below and detailed in the following figure:

- Equipment of excellence, EQUIPEX (very high quality scientific facilities)
- Laboratories of Excellence, LABEX (internationally visible labs)
- Research Hospitals, IHU (centers of excellence in research, care, training and technology transfer in the health field)
- Cohort (long-term funding for cohorts with underlying health issues)
- Preindustrial Biotechnology Demonstrators (allowing faster achievement of the proof of commercial concept)
- National Infrastructures in Health and Biotechnology
- Hospital University research in Health, RHU (supporting translational health research projects or clinical research project)

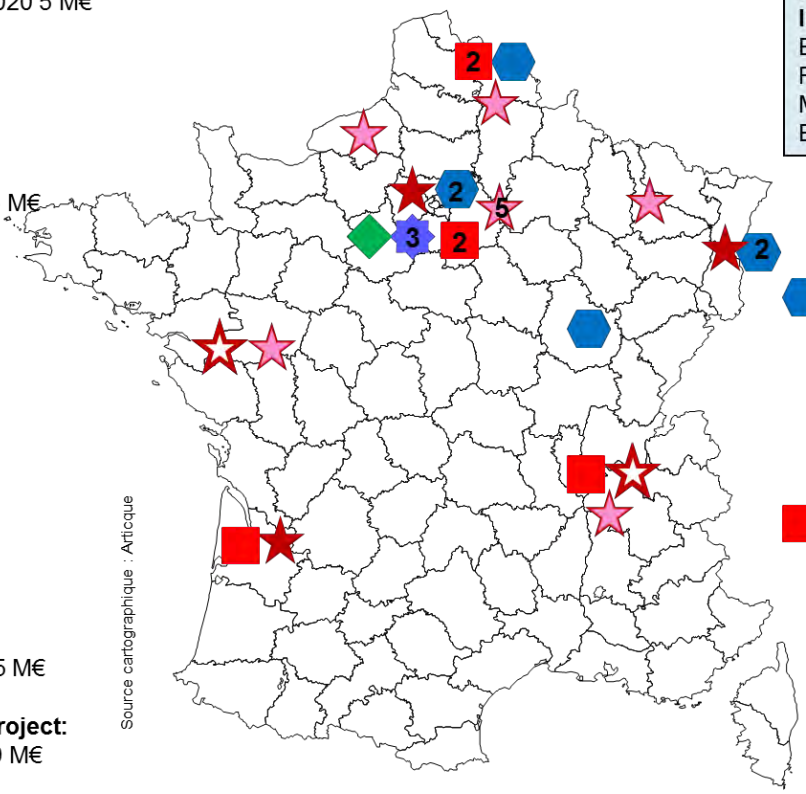
RHU:
BIOART-LUNG 2020 5 M€
FIGHT-HF 9 M€
CARMMA 9 M€
CHOPIN 8,3 M€
iLite 8,5 M€
iVASC 8,5 M€
iMAP 9 M€
MARVELOUS 5,5 M€
PreciNASH 6 M€
STOP-AS 6,6 M€

IHU:
ICAN 45 M€
LIRYC 45 M€
MixSurg 67,3 M€

Promising IHU:
OPERA
CESTI

Cohorts:
CKD rein 4 M€
E4N 7,9 M€
CONSTANCES 35 M€

Demonstration project:
MetaGenoPolis 19 M€



Source cartographique : Articque

National Infrastructures:
Biobanques 17 M€
F-CRIN 18 M€
MetaboHub 10 M€
ECELLFRANCE 12 M€

Labex:
EGID 18 M€
INFLAMEX 9 M€
LipStic 6 M€
LERMIT 19 M€
Mitocross 5,5 M€
Hepsys 3 M€

Equipex:
IVTV 2,7 M€
LIGAN 8 M€
MUSIC 3 M€
RE-CO-NAI 13 M€
ImaginExBioMed 6,8 M€
HEPATHER 10 M€

Circulatory system

Thierry COUFFINHAL

Biology of Cardiovascular Diseases

University of Bordeaux
Inserm UMR1034
Thierry COUFFINHAL
Pessac

Our team combine tools of genetics, in vivo and in vitro experiments and imagery to characterize and follow in time and space the role of target genes in the vascular and thrombosis function.

Key facts

Team

• Researchers : 3
• Technicians : 7
• Postdoc fellows : 1
• PhD Students : 7

Translational approaches

• Patents : 3
• Clinical research grants : 1
• Industry partnerships : 0

International research links

• MARHL Marko - Slovénie; STARK Konstantin - Allemagne;
• MRAICHE Fatima - Qatar; JOSEFSSON Emma - Australie; BECHER Harald - Royaume-Uni
• FLIEGEL Larry - Canada; WEHBE Katia - Royaume-Uni

Keywords

• Cardiovascular diseases
• Vascular biology
• Endothelial function
• Animal models
• Experimental animal models
• Vessel imaging
• Vascular cell culture
• Molecular and cellular biology

Biological Resources

• IMAGING: White field and fluorescent microscopy; Confocal microscopy; Time lapse microscopy; Rapid film imaging; Perfusion imaging (laser Doppler); Xray tomography; Infrared imaging
• IN VITRO: Cell culture; In vitro models; Biochemistry; Molecular Biology; Histology; Analysis
• CLINICS: Pharmacology
• IN VIVO: Transgenic mice; Mouse experimental models; Measurement of physiologic cardiovascular parameters; Thrombosis; Pig experimental models

Research Brief :

Clinical and basic research demonstrates that the endothelium plays a crucial role in mediating homeostasis and is involved in virtually every disease, either as a primary determinant of pathophysiology or as a victim of collateral damage. The endothelium is involved in the maintenance of normal organs and vascular structure and function. It may be thought as an organ by itself. Following its abnormalities in function would provide a tremendous opportunity to inform about the status of the disease progression. As it is widely distributed and easily accessible, it may be regarded as critical target in the fight against some cardiovascular ischemic diseases.
Our project aims to improve endothelium knowledge and how endothelium interacts with its microenvironment. We are interested in understanding endothelial machinery in the control of vessel maintenance and function in different pathological settings:
- Role of endothelial dysfunction in heart failure with preserved ejection fraction
- Role of endothelial dysfunction in critical hind limb ischemia
- Endothelial cells, blood-brain barrier dysfunction in cerebrovascular disease
- Retinopathy and vascular lesions
- Role of endothelial cells in thrombosis ? example of myeloproliferative neoplasms
Wnt/Frizzled, Hedgehog and JAK2 signaling pathways are specifically studied in endothelial dysfunction.

• **Methodologies Used :**

Molecular and cellular biology
Cell culture: vascular cell proliferation, directional migration, cell velocity, videomicroscopy, 2-D and 3-D, adhesion, NETs, angiogenesis models, hypoxia models; Platelets, megacaryopiesis
Biochemistry
Vessel imaging: microscanner (microCt), confocal microscopy, 3D image reconstruction
Experimental animal models: conditional knock-out mouse models, model of hindlimb ischemia, infarctus and ischemia reperfusion, oxygen induced retinopathy, corneal angiogenesis, Thrombosis models

Publications

Sewduth Raj Nayan, Jaspard-Vinassa Béatrice, Peghaire Claire, Guillabert-Gourgues Aude, Franzl Nathalie, Larrieu-Lahargue Frédéric, Moreau Catherine, Fruttiger M., Dufourcq Pascale, Couffinhal Thierry and Duplaa Cécile (2014). The ubiquitin ligase PDZRN3 is required for vascular morphogenesis through Wnt/planar cell polarity signalling, Nature Communications. 5(4832),

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R. Markovic, J. Peltan, M. Gosak, D. Horvat, B. Zalik, B. Seguy, R. Chauvel, G. Malandain, T. Couffinhal, C. Duplaa, M. Marhl, and E. Roux (2017). Planar Cell Polarity Genes Frizzled4 and Frizzled6 Exert Patterning Influence on Arterial Vessel Morphogenesis, PLoS One. (12),

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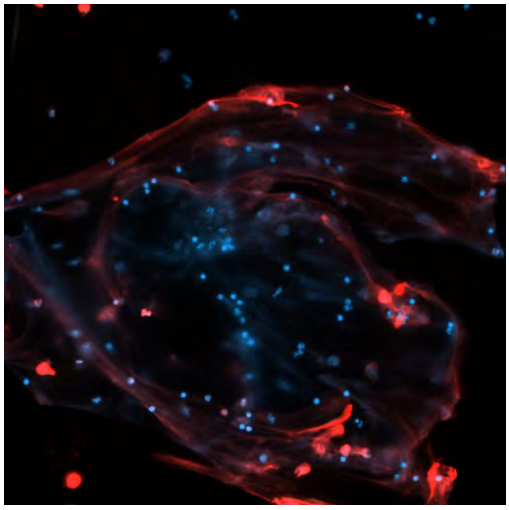
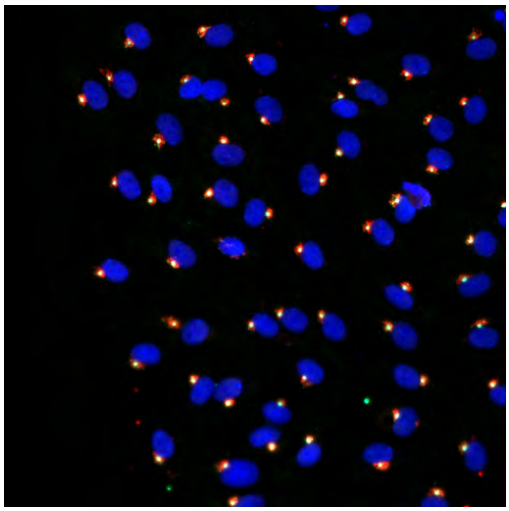
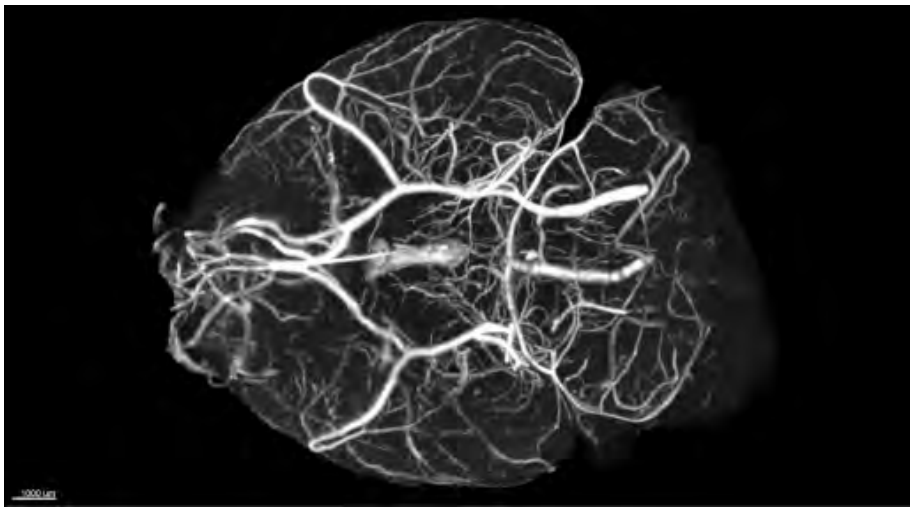
Neutrophil extracellular traps in patients with JAK2V617F positive myeloproliferative neoplasms



Endothelial polarization



3D visualisation of mouse cerebral vascularisation (microscanner)



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Key facts

Team

- Researchers : 8
- Technicians : 5
- Postdoc fellows : 1
- PhD Students : 3

Translational approaches

- Patents : 1
- Clinical research grants : 4
- Industry partnerships : 3

Keywords

- Oxidized LDL
- cell signalling
- apoptosis
- proliferation
- angiogenesis
- mitophagy, autophagy
- Atherosclerosis
- plaque imaging
- Lipid peroxidation
- molecular and cellular biology techniques
- transplantation animal model
- biological biomarkers

Anne Negre-Salvayre Cécile Vindis

Lipid Peroxidation, Signaling and Vascular Diseases

Université de Toulouse 3
(Université Paul Sabatier)
Inserm U 1048
Angelo Parini
Toulouse

The team is leader in basic fundamental research on lipid peroxidation signalling in vascular cells, animal models for atherosclerosis and transplant vasculopathy and translational studies on circulating biomarkers for the follow-up of coronary patients

Research Brief :

Low density lipoproteins (LDL) in the vascular wall play a key-role in the early stages of atherogenesis. Oxidized lipids participate in the development of lesions by promoting local inflammatory response, smooth muscle cell migration and proliferation, extracellular matrix production and plaque remodeling. Oxidized lipid properties depend on their local concentration, nature or uptake by scavenger receptors (CD36, LOX-1, SRA...), which contribute to fragilize the lesions, promote plaque erosion or rupture and finally lead to athero-thrombosis events.
Our team aims at deciphering the mechanisms evoked by oxidized lipids, implicated in the balance cell survival/death. This includes the ceramide/sphingosine-1-phosphate rheostat, which constitutes a key-mechanism for neoangiogenesis, endoplasmic reticulum stress, and cytosolic calcium dysregulation, We investigate the role of antioxidant and antiapoptotic defense systems such as Nrf2, autophagy and mitophagy, and the modification of cellular proteins by lipid peroxidation products which alter their function and contribute to apoptosis.
Our objectives are to i/ characterize the role of oxidized lipids in neoangiogenesis, vascular aging, calcification of advanced plaques, and the protective role of autophagy, (ii) developing innovative computational vascular medical imaging techniques for visualizing vascular hemodynamics and wall shear stress, and (iii) identifying new non-invasive biomarkers for the coronary patient follow-up.

• Methodologies Used :

Vascular cell culture (primary culture and cell lines). LDL isolation and oxidation.
Oxidative stress: Intracellular ROS increase, TBARS, 4-HNE, ONE, acrolein, carbonyl protein content
Apoptosis, flow cytometry, TUNEL, calcium, immunocyto/histochemistry, mitochondria
Cell migration, proliferation, enzyme activities, protein characterization, proteomics
Microarrays, siRNAs, Q-PCR. Animal models for transplant vasculopathy, angiogenesis, atherosclerosis, mutant mice, plaque imaging

Publications

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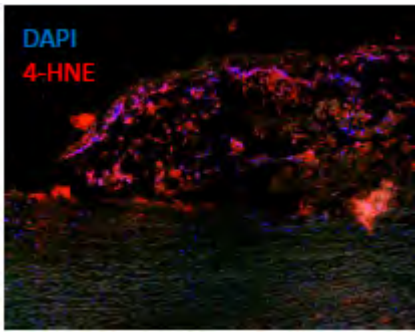
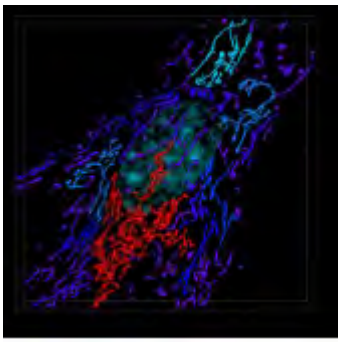
Expression of hydroxynonenal-adducts in human atherosclerosis lesions



Mitophagy monitoring in oxidized LDL stimulated human VSMC



Negre-Salvayre Anne - Anne.Negre-Salvayre@inserm.fr

Jean-Michel Senard
Céline Galés

Molecular and clinical determinants of cardiac architecture

Université de Toulouse 3
(Université Paul Sabatier)
Inserm 1048
Angelo Parini
Toulouse

Key facts

Team

- Researchers : 12
- Technicians : 2
- Postdoc fellows : 1
- PhD Students : 5

Translational approaches

- Patents : 2
- Clinical research grants : 3
- Industry partnerships : 3

Keywords

- cardiac regeneration
- cardiac tissue architecture
- ephrine-B1
- GPCRs
- biased agonism
- BRET/FRET
- atomic force microscopy
- electron microscopy

Biological Resources

- mice models
- patients cohorts
- cell lines

The translationnal projects of the team are based on original methods for sympathetic nervous sytem acitvity recording and pharmacology of related GPCRs

Research Brief :

The physiologic response of an organ basically relies on a complex interplay between the different cell types structuring its tissue. At the cellular level, the response arises from the plasma membrane through different receptors, channels, pumps? that integrate and process the extracellular stimuli (chemical, mechanical). Alteration of the plasma membrane response is the hallmark of a number of pathological conditions. Now, how the plasma membrane and the overall cell architecture behave in such pathologies and what is the impact on the surface organization and functions of the proteins inserted in the plasma membrane still remain poorly understood. This is however of major interest in pharmacological medicine since most marketed drugs target these plasma membrane proteins.

In this context, the research program of our team focuses on understanding the relationship between the architecture of cardiac tissue (more precisely of the cardiac contractile cells) on the function and pharmacology of the heart and but also on the brain.
Our specific interests are subdivided in three main projects all around the notion of heart architecture:
Ø Identification of the molecular determinants of adult cardiomyocyte morphology & cardiac tissue organization
Ø Characterization of the Heart / Brain axis
Ø Exploration of cardiac cell surface GPCR architecture as a molecular basis underlying biased agonism efficacy of ligands (pharmacology of GPCR).

- **Methodologies Used :**

Muscle and renal sympathetic nerve activity(animals and humans)
Blood pressure and heart rate variability
Cardiovascular phenotying including histomorphology
Bioluminescent resonance energy transfer applied to GPCRs study

Publications

Franchitto N, Despas F, Labrunée M, Roncalli J, Boveda S, Galinier M, Senard JM, Pathak A. (2010). Tonic chemoreflex activation contributes to increased sympathetic nerve activity in heart failure-related anaemia., Hypertension. 55(4), 1012-1017

Saulière A, Bellot M, Paris H, Denis C, Finana F, Hansen JT, Altié MF, Seguelas MH, Pathak A, Hansen JL, Sénard JM, Galés C (2012). Deciphering biased-agonism complexity reveals a new active AT1 receptor entity., Nature chemical biology. 8(7), 622-30

Genet G, Guilbeau-Frugier C, Honton B, Dague E, Schneider MD, Coatrieux C, Calise D, Cardin C, Nieto C, Payré B, Dubroca C, Marck P, Heymes C, Dubrac A, Arvanitis D, Despas F, Altié MF, Seguelas MH, Delisle MB, Davy A, Sénard JM, Pathak A, Galés C (2012). Ephrin-B1 is a novel specific component of the lateral membrane of the cardiomyocyte and is essential for the stability of cardiac tissue architecture cohesion., Circulation research. 110(5), 688-700

34. DAGUE E, GENET G, LACHAIZE V, GUILBEAU-FRUGIER C, FAUCONNIER J, MIAS C, PAYRÉ B, CHOPINET L, ALSTEENS D, KASAS S, SEVERAC C, THIREAU J, HEYMES C, HONTON B, LACAMPAGNE A, PATHAK A, SÉNARD JM, GALÉS C (2014). Atomic force and electron microscopic-based study of sarcolemmal surface of living cardiomyocytes unveils unexpected mitochondrial shift in heart failure., J Mol Cell Cardiol. 74(), 162-172

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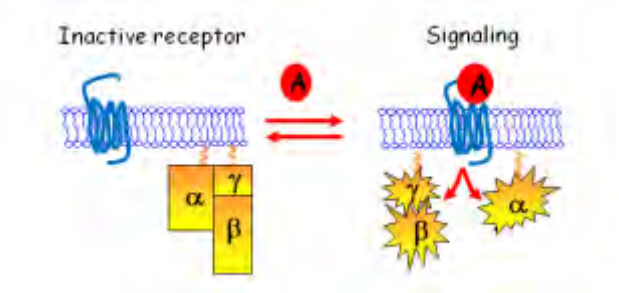
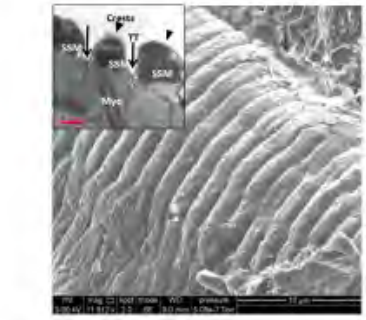
5. GALANDRIN S, DENIS C, BOULARAN C, MARIE J, M'KADMI C, PILETTE C, DUBROCA C, NICAISE Y, SEGUELAS MH, N'GUYEN D, BANÈRES JL, PATHAK A, SÉNARD JM, GALÉS C (2016). Cardioprotective Angiotensin-(1-7) Peptide Acts as a Natural-Biased Ligand at the Angiotensin II Type 1 Receptor., Hypertension. 68(6), 1365-1374

BRET biosensor sensing G protein activation



Basics of biosensors for G protein activation sensing using BRET technology

nanoscale imaging of normal cardiomyocyte



Electron microscopy picture showing the organization of the lateral membrane of normal cardiomyocyte depicting the periodic presence of crests. Inset: subsarcolemmal mitochondria under the crests

Key facts

Team

• Researchers : 3
• Technicians : 1
• Postdoc fellows : 2
• PhD Students : 5

Translational approaches

• Patents : 8
• Clinical research grants : 1
• Industry partnerships : 3

Keywords

• Signalling
• senescence
• Heart failure
• Cyclic AMP
• Monoamine-oxidase A
• Epigenetic
• Biochemistry
• Molecular biology
• viral gene transfer
• genetically modified mice
• Chip seq

Biological Resources

• animal models of cardiac hypertrophy, myocardial infarctus and arrhythmia.
• Epac, MAO transgenic and knowckout mice

Frank Lezoualc'h

Signalling and pathophysiology of heart failure

Université de Toulouse, Paul Sabatier
Inserm UMR-1048
Angelo Parini
Toulouse

Our team is specialized in the functional characterization and signaling of the cyclic AMP-binding Epac, Carabin and monoamine oxidase-A in the cardiovascular system. Our aim is to identify new therapeutical targets for the treatment of heart failure.

Research Brief :

Our team entitled "Signalling and pathophysiology of heart failure" associates clinicians and researchers sharing a common scientific background and interest in understanding the molecular and cellular mechanisms involved in Heart Failure (HF). The final objective is to identify relevant targets to prevent or reverse HF.
We have identified new signaling pathways involved in cardiac hypertrophy and failure. These signaling events involve the cAMP-binding proteins Epac and Carabin that couple membrane receptors to pathological cardiac remodeling. It also involves involves the metabolism of catecholamines by monoamine oxidase-A (MAO-A) as a source of reactive oxygen species (ROS) in HF and cardiac aging. Our goal now is to dissect the signaling pathways of Epac/Carabin/MAO-A in order to understand how these proteins influence cell fate. We will analyze their target genes and epigenetic mark during cardiac remodeling. Our efforts also aim at better understanding the importance of MAO-A/ROS axis in the development of HF associated with aging.
Our approach is multidisciplinary: we are seeking pharmacological modulators of these therapeutic targets (in silico screening and HTS) and develop mouse lines and gene therapy vectors to identify their role in the myocardium. Our methodologies combine cell culture, cell imaging, biochemical assays, mass spectrometry, molecular biology (RNA Seq, ChIP-Seq, ..) and experimental models of heart failure.

• **Methodologies Used :**

Molecular and cellular biology methods (PCR, immunocytochemistry, cell culture (neonatal cardiac myocytes, adult cardiac myocytes, cell lines), infection and transfection,
Biochemistry (Immunoblot, immunoprecipitation, affinity precipitation assay, 2-D gel)
RNAseq & ChipSeq
Calcium imaging
Experimental animal models (conditional knock-out mouse models, models of cardiac hypertrophy and failure)

Publications

Courilleau D, Bisserier M, Jullian JC, Lucas A, Bouyssou P, Fischmeister R, Blondeau JP, Lezoualc'h F (2012). Identification of a Tetrahydroquinoline Analog as a Pharmacological Inhibitor of the cAMP-binding Protein Epac., The Journal of biological chemistry. 287(53), 44192-202

Villeneuve C, Guilbeau-Frugier C, Sicard P, Lairez O, Ordener C, Duparc T, De Paulis D, Couderc B, Spreux-Varoquaux O, Tortosa F, Garnier A, Knauf C, Valet P, Borchi E, Nediani C, Gharib A, Ovize M, Delisle MB, Parini A, Mialet-Perez J. (2013). p53-PGC-1alpha pathway mediates oxidative mitochondrial damage and cardiomyocyte necrosis induced by monoamine oxidase-A upregulation: role in chronic left ventricular dysfunction in mice., Antioxid Redox Signal.. 18(1), 5-18

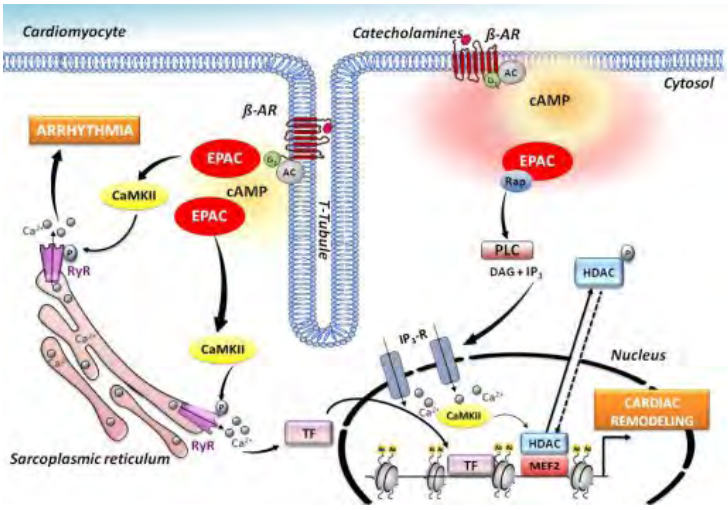
Bisserier M, Berthouze-Duquesnes M, Breckler M, Tortosa F, Fazal L, de Régibus A, Laurent AC, Varin A, Lucas A, Branchereau M, Marck P, Schickel JN, Deloménie C, Cazorla O, Soulas-Sprauel P, Crozatier B, Morel E, Heymes C, Lezoualc'h F. (2015). Carabin protects against cardiac hypertrophy by blocking calcineurin, Ras, and Ca2+/calmodulin-dependent protein kinase II signaling., Circulation. 131(4), 390-400

Santin Y, Sicard P, Vigneron F, Guilbeau-Frugier C, Dutaur M, Lairez O, Couderc B, Manni D, Korolchuk VI, Lezoualc'h F, Parini A, Mialet-Perez J (2016). Oxidative Stress by Monoamine Oxidase-A Impairs Transcription Factor EB Activation and Autophagosome Clearance, Leading to Cardiomyocyte Necrosis and Heart Failure, Antioxid Redox Signa. 25(1), 10-27

Lezoualc'h F, Fazal L, Laudette M, Conte C (2016). Cyclic AMP Sensor EPAC Proteins and Their Role in Cardiovascular Function and Disease, Circulation research. 118(5), 881-897

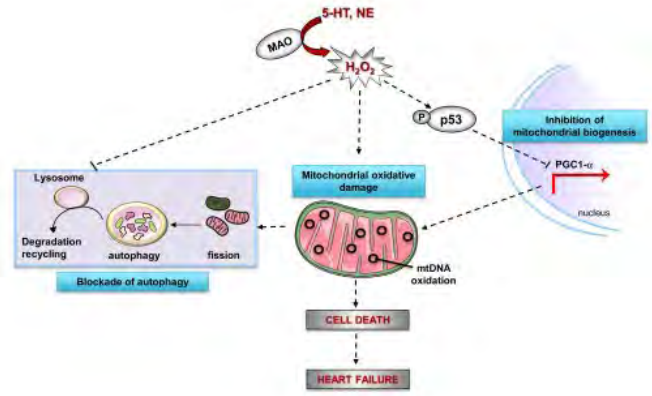
Fazal L, Laudette M, Paula-Gomes S, Pons S, Conte C, Tortosa F, Sicard P, Sainte-Marie Y, Bisserier M, Lairez O, Lucas A, Roy J, Ghaleh B, Fauconnier J, Mialet-Perez J, Lezoualc'h F (2017). The Multifunctional Mitochondrial Epac1 Controls Myocardial Cell Death, Circulation research. 120(4), 645-47

Epac signalling leads to pathological cardiac remodeling and heart failure



Beta-adrenergic receptors (B-AR) activate Epac which induces Ca2+ dysregulation via the ryanodine receptor (RyR) leading to arrhythmia. Epac also regulates the activity of transcription factors (TF) which are involved in pathological cardiac remodelling.

Deleterious effect of MAO-A on mitochondrial damage, cardiomyocyte death and heart failure.



MAO-A-generated oxidative stress triggers p53 activation leading to down-regulation of peroxisome proliferator-activated receptor-gamma coactivator-1a (PGC-1a), a master regulator of mitochondrial biogenesis. On the other hand, MAO-A-generated oxidative stress impairs lysosome function and acidification leading to autophagic flux blockade and altered mitochondrial quality control

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Daniel Henrion

Cardiovascular Mechanotransduction (CarMe)

Université d' Angers
Inserm U1083 CNRS UMR 6015
Daniel Henrion
Angers

Key facts

Team

- Researchers : 12
- Technicians : 5
- Postdoc fellows : 2
- PhD Students : 10

Translational approaches

- Patents : 2
- Clinical research grants : 4
- Industry partnerships : 4

International research links

- Germany, Gret-Britain, USA, Spain, Canada, Hungary

Keywords

- blood flow
- ischemia/reperfusion
- GPCRs
- endothelium
- mechanotransduction
- Microcirculation
- lim ischemia
- confocal microscopy
- resistance arteries
- bio-computing
- Local blood flow
- electrophysiology

Study of small resistance arteries mechanotransduction in ischemic diseases (limb and heart ischemia, hypertension, diabetes, obesity)

Research Brief :

Resistance arteries are located upstream capillaries, are crucial to the delivery of blood to vital tissues at relevant flow and pressure. Disorders of these small arteries can raise capillary pressure and cause downstream organ damage such as that seen in diabetes, neurovascular disorders or kidney disease. We aim a) to define how structure and function of small arteries change in ischemic disorders associated with ageing and the related risk factors and aa) to identify the specific changes in pathways involved in resistance artery homeostasis leading to the identification of novel targets/biomarkers for intervention and disease prevention.
We have 3 specific objectives:
1- investigate flow-mechanotransduction in resistance arteries in order to better define the pathways involved with a special focus on the mechanosensitive channels and on the mechanosensitive receptors.
2- determine in resistance arteries the mechanism of remodelling involved in ischemic disorders
3- investigate the mechanisms involved in ischemia-reperfusion injury and to bring forward new strategies to prevent its occurrence.
Finally, ischemic disorders are investigated using mouse models of ischemia/reperfusion in healthy and diseased ageing and in human vessels from patients with severe limb ischemia and healthy volunteers.

Methodologies Used :

Arteriography and myography for resistance arteries (in vitro function)
In vivo microcirculatory function (Laser-Doppler flow metry, arteriography...)
Molecular biology of resistance arteries and mitochondria
electrophysiology (patch-clamp on tissue slices, microelectrodes on xen. oocytes)
confocal microscopy (fixed tissues and real-time)
Molecular modeling and dynamics, bioinformatics

Publications

Freidja ML, Tarhouni K, Toutain B, Fassot-Lucht C, Loufrani L, Henrion D (2012). The AGE-Breaker ALT-711 Restores High Blood Flow-Dependent Remodeling in Mesenteric Resistance Arteries in a Rat Model of Type 2 Diabetes, Diabetes. 611(), 1562-72

Retailleau K, Toutain B, Galmiche G, Fassot C, Sharif-Naeini R, Kauffenstein G, Mericskay M, Duprat F, Grimaud L, Merot J, Lardeux A, Pizard A, Baudrie V, Jeunemaitre X, Feil R, Göthert JR, Lacolley P, Henrion D, Li Z, Loufrani L (2013). Selective involvement of serum response factor in pressure-induced myogenic tone in resistance arteries, Arterioscler Thromb Vasc Biol.. 33(), 339-46

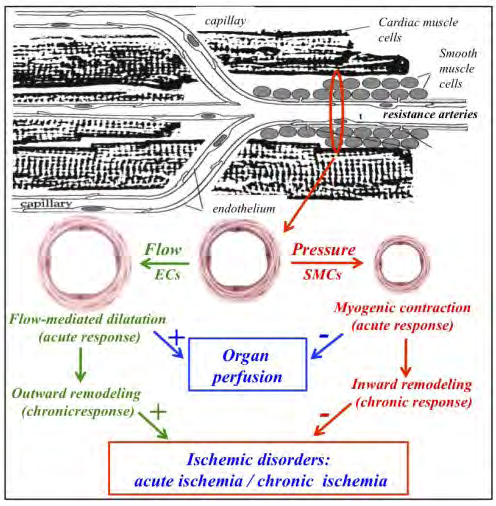
Tarhouni K, A.L. Guihot, E. Vessières, B. Toutain, V. Procaccio, L Grimaud, L. Loufrani, F. Lenfant, JF. Arnal, Henrion D (2014). Determinants of flow-mediated outward remodeling in female rodents: respective roles of age, estrogens and timing, Arterioscler Thromb Vasc Biol.. 347(), 1281-9

Le Page S, Niro M, Fauconnier J, Cellier L, Tamareille S, Gharib A, Chevrollier A, Loufrani L, Grenier C, Kamel R, Sarzi E, Lacampagne A, Ovize M, Henrion D, Reynier P, Lenaers G, Mirebeau-Prunier D, Prunier F (2016). Increase in Cardiac Ischemia-Reperfusion Injuries in Opa1+/- Mouse Model, PLoS One. 11(10), e0164066

Caillon A, Grenier C, Grimaud L, Vessieres E, Guihot AL, Blanchard S, Lelievre E, Chabbert M, Foucher ED, Jeannin P, Beauvillain C, Abraham P, Loufrani L, Delneste Y, Henrion D (2016). The angiotensin II type 2 receptor activates flow-mediated outward remodelling through T cells-dependent interleukin-17 production, Cardiovascular research. 8112(1), 515-25

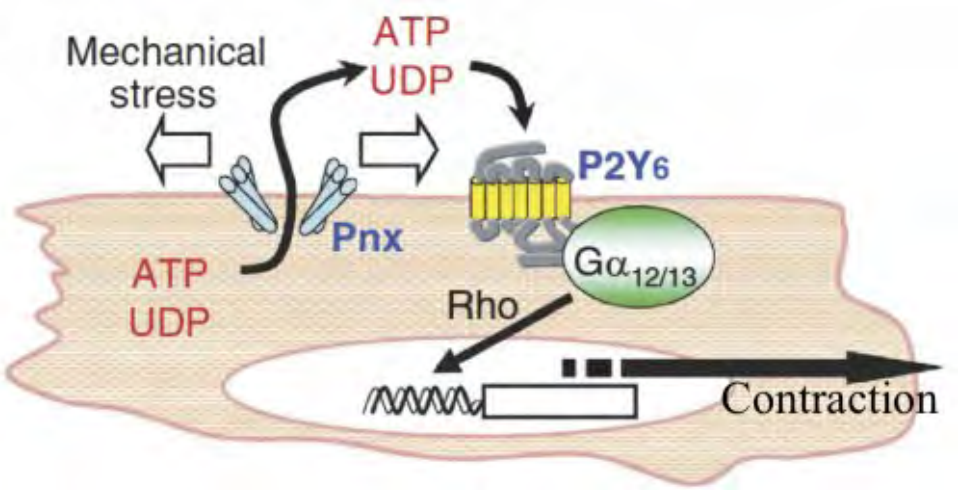
Kauffenstein G, Tamareille S, Prunier F, Roy C, Ayer A, Toutain B, Billaud M, Isakson BE, Grimaud L, Loufrani L, Rousseau P, Abraham P, Procaccio V, Monyer H, de Wit C, Boeynaems JM, Robaye B, Kwak BR, Henrion D (2016). Central Role of P2Y6 UDP Receptor in Arteriolar Myogenic Tone, Arterioscler Thromb Vasc. 36(), 1598-1606

Vascular response to pressure and flow



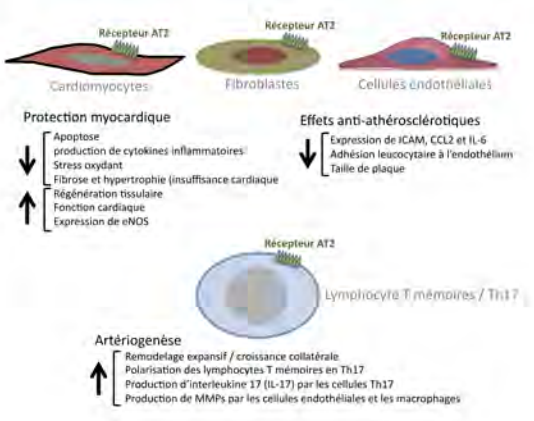
Acute and chronic vascular response to pressure and flow determine a proper tissue perfusion. A desiquilibrium between pressure- and flow-dependent tone and wall structure is involved in cardiovascular disorders. From www.bnmi. fr (team 2: CarMe)

Purinergic signalling in myogenic tone.



In small arteries, blood pressure activated ATP output from smooth muscle cells leading to P2Y6 receptor stimulation, RhoA activation and contraction (myogneic tone). Kauffenstein et al. Arterioscler Thromb Vasc Biol. 2016;36:1598-1606.

Vascular effects of the angiotensin II type 2 receptor



From Caillon et al., Cardiovasc Res. 2016;112(1):515-25

Henrion Daniel - daniel.henrion@inserm.fr - http://mitovasc.univ-angers.fr/

Key facts

Team

• Researchers : 18
• Technicians : 6
• Postdoc fellows : 0
• PhD Students : 17

Translational approaches

• Patents : 2
• Clinical research grants : 7
• Industry partnerships : 5

International research links

• ERANET : Netherlands, Poland, Belgium, Spain - OTHER: Finland, Germany

Keywords

• endothelium
• lymphatics
• aortic stenosis
• heart failure
• transcatheter aortic valve implantation (TAVI)
• vascular echo-tracking
• myograph
• echocardiography
• magnetic resonance imaging
• arteriograph

Biological Resources

• patients : heart failure, septic shock, antiphospholipid syndrome, hypertension, diabetes, polycystic kidney disease, kidney transplantation.

Vincent Richard

EnVI; Endothelium, Valvulopathy and Heart Failure

Rouen Normandy University
Inserm U1096
Vincent Richard
Rouen

Unique translational (both experimental and clinical) expertise in the functional evaluation of vascular and cardiac dysfunction, major innovation in the field of aortic stenosis, unique research on cardiac lymphatics

Research Brief :

Our cardiovascular research focuses on 3 aspects: vascular protection, treatment of aortic stenosis and improvement of cardiac contractile function/reduction of heart failure. This research is translational, performed both in experimental/pre-clinical models and in humans (healthy volunteers and patients).
Our vascular research concerns protection of vascular endothelial cells against injury or dysfunction induced by risk factors (hypertension, diabetes) or cardiovascular diseases (myocardial infarction, heart failure, septic shock etc.). Pharmacological targets currently evaluated include in particular protein tyrosine phosphatase 1B, soluble epoxide hydrolase, and dopamine receptors
Regarding aortic stenosis, our work is based on the Rouen discovery and development of transcatheter aortic valve implantation (TAVI); we attempt to uncover new mechanisms and new pathways for prevention or slowing of aortic stenosis development. We also address the links between endothelial dysfunction and aortic stenosis. This research is performed within the frame of the FHU REMOD-VHF and RHU STOP-AS both placed under the leadership of our group.
Finally, our cardiac research concerns the evaluation of new treatments of diastolic dysfunction or heart failure and the cardiac consequences of aortic stenosis or its reversion. In particular, we focus on the benefits of lymphangiogenic therapy in heart failure, within the frame of an ERA-NET project under our leadership.

• **Methodologies Used :**

- Experimental and clinical cardiac and vascular imaging (echocardiography, echo-tracking, tonometry, tissue Doppler, Holter)
- Magnetic resonance imaging for small animals
- In vitro vascular functional evaluation (arteriograph, myograph)
- Experimental models of cardiovascular diseases in rats and mice (myocardial infarction, heart failure, hypertension, aortic stenosis, insulin resistance etc.)
- Evaluation of oxidative stress
- culture aortic valve cells
- evaluation of cardiac lymphatic network & lymphangiography

Publications

Banquet S, Gomez E, Nicol L, Edwards-Lévy F, Henry JP, Cao R, Schapman D, Dautreaux B, Lallemand F, Bauer F, Cao Y, Thuillez C, Mulder P, Richard V, Brakenhielm E. (2011). Arteriogenic therapy by intramyocardial sustained delivery of a novel growth factor combination prevents chronic heart failure., CIRCULATION. 124(1059), 1069

Eltchaninoff H, Prat A, Gilard M, Leguerrier A, Blanchard D, Fournial G, Iung B, Donzeau-Gouge P, Tribouilloy C, Debrux JL, Pavie A, Gueret P; FRANCE Registry Investigator (2011). Transcatheter aortic valve implantation: early results of the FRANCE (FRench Aortic National CoreValve and Edwards) registry., EUROPEAN HEART JOURNAL. 32(191), 197

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Lorthioir A, Joannidès R, Rémy-Jouet I, Fréguin-Bouilland C, Iacob M, Roche C, Monteil C, Lucas D, Renet S, Audrézet MP, Godin M, Richard V, Thuillez C, Guerrot D, Bellien J. (2015). Polycystin deficiency induces dopamine-reversible alterations in flow-mediated dilatation and vascular nitric oxide release in humans., KIDNEY INTERNATIONAL. 87(465), 1472

Maupoint J, Besnier M, Gomez E, Bouhzam N, Henry JP, Boyer O, Nicol L, Mulder P, Martinet J, Richard V. (2016). Selective Vascular Endothelial Protection Reduces Cardiac Dysfunction in Chronic Heart Failure, CIRCULATION HEART FAILURE. 9(e002895), e002895

Henri O, Pouehe C, Houssari M, Galas L, Nicol L, Edwards-Lévy F, Henry JP, Dumesnil A, Boukhalfa I, Banquet S, Schapman D, Thuillez C, Richard V, Mulder P, Brakenhielm E. (2016). Selective Stimulation of Cardiac Lymphangiogenesis Reduces Myocardial Edema and Fibrosis Leading to Improved Cardiac Function Following Myocardial Infarction., CIRCULATION. 133(1484), 1497

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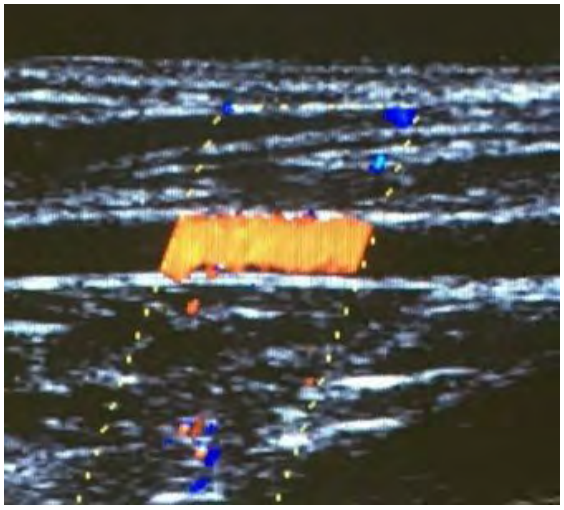
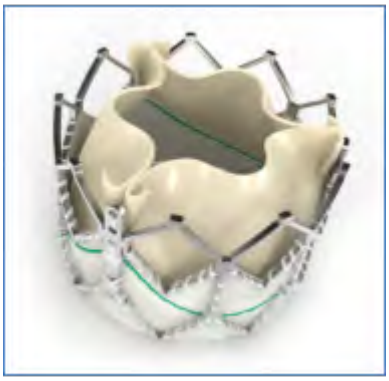
noninvasive evaluation of human arterial diameter



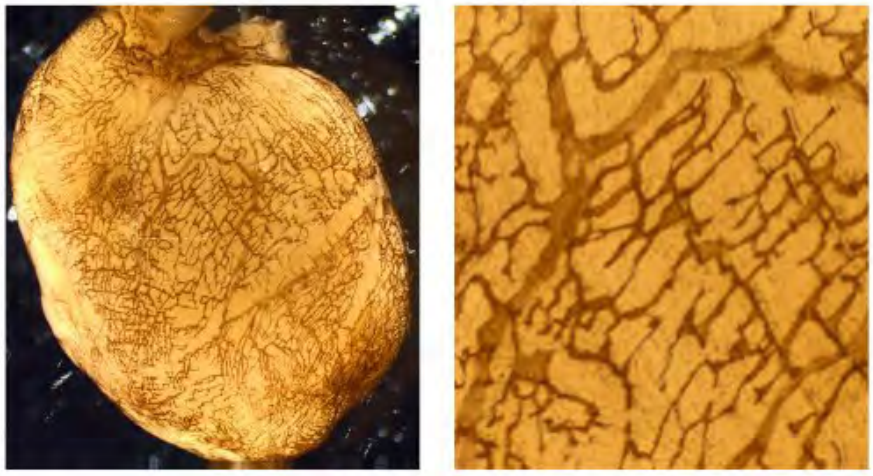
Non invasive, dynamic, echo-tracking based imaging of human radial artery diameter, allowing evaluation of changes in vascular tone and thus of endothelial-dependent dilatation and endothelial dysfunction

Transcatheter Aortic Valve



Aortic Valve designed for Transcatheter Aortic Valve Implantation (TAVI)

Cardiac lymphatics network



Immunohistochemical imaginf of cardiac lymphatic network (rat left ventricle)

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Flavien Charpentier

Ion channels and cardiac arrhythmias

Université de Nantes
Inserm UMR1087 CNRS UMR6291
Richard Redon
Nantes

The strength of our team relies on the diversity of its members, from biophysicists and cell biologists to clinical electrophysiologists, and its strong collaboration with the team of genetics and cardiologists, allowing the development of gene-to-bedside research programs on cardiac arrhythmias.

Key facts

Team

- Researchers : 11
- Technicians : 7
- Postdoc fellows : 0
- PhD Students : 8

Translational approaches

- Patents : 0
- Clinical research grants : 2
- Industry partnerships : 1

Keywords

- ion channel
- cardiac conduction
- cardiac arrythmia
- Brugada syndrome
- long QT syndrome
- channelopathies
- aging
- animal models
- in vivo electrophysiology
- DGE-Seq, RNA-Seq
- cellular electrophysiology
- proteomics
- human induced pluripotent stem cell

Biological Resources

- cardiac myocytes and fibroblasts in primary culture
- human induced pluripotent stem cell lines of genetically inherited arrhythmias
- original transgenic mouse models of arrhythmias

Research Brief :

Our team projects are based on our expertise in cardiac arrhythmias and in heart cell biology and differentiation of human induced pluripotent stem (iPS) cells into cardiomyocytes. Our goal is to understand the function and regulation of cardiac ion channels in physiological conditions and in the context of cardiac arrhythmias, to identify new therapeutic targets.
Our strategy is organized around 4 main research programs:
1. Cardiac arrhythmias and sudden death (I. Baró & N. Gaborit)
The goal is to identify pathophysiological mechanisms of hereditary cardiac arrhythmias, based on cellular models developed from patient induced pluripotent stem cells and knock-in mouse models
2. Fibrosis and cardiac conduction diseases (F. Charpentier)
This program aims to identify therapeutic targets based on the signaling pathways that we have shown to be involved in the development of fibrosis during aging in hereditary progressive cardiac conduction diseases
3. Post-translational regulation of Nav1.5 (C. Marionneau)
We are evaluating the involvement of the phosphorylation sites that we identified by a phosphoproteomic approach on Nav1.5 in the posttranslational regulation of this channel
4. Cardiac ionic channels: from biophysics to therapeutic applications (G. Loussouarn)
This program aims to develop therapeutic tools targeting the peptide sequences controlling the opening of voltage-gated ion channels involved in cardiac channelopathies.

- **Methodologies Used :**

Molecular and cellular biology: Taqman low density arrays, RNA-Seq, DGE-Seq, ChIP-Seq immunostaining, time laps videomicroscopy
Proteomics: pull-down assay, yeast two-hybrid interaction assay, in-solution mass spectrometry
Electrophysiology: conventional and high-throughput automated (384 wells) patch-clamp, high-throughput action potential recording with voltage-sensitive dyes, microelectrodes, MultiElectrode Arrays, electrocardiogram, in vivo intracardiac recording and pacing, telemetry
Target discovery and pharmacological screening

Publications

Laurent G, Saal S, Amarouch MY, Béziau DM, Marsman RF, Faivre L, Barc J, Dina C, Bertaux G, Barthez O, Thauvin-Robinet C, Charron P, Fressart V, Maltret A, Villain E, Baron E, Mérot J, Turpault R, Coudière Y, Charpentier F, Schott JJ, Loussouarn G, Wilde AA, Wolf JE, Baró I, Kyndt F, Probst V. (2012). Multifocal ectopic Purkinje-related premature contractions: a new SCN5A-related cardiac channelopathy., Journal of the American College of Cardiology. 60(2), 144-56

Jouni M, Si-Tayeb K, Es-Salah-Lamoureux Z, Latypova X, Champon B, Caillaud A, Rungoat A, Charpentier F, Loussouarn G, Baró I, Zibara K, Lemarchand P, Gaborit N. (2015). Toward Personalized Medicine: Using Cardiomyocytes Differentiated From Urine-Derived Pluripotent Stem Cells to Recapitulate Electrophysiological Characteristics of Type 2 Long QT Syndrome., Journal of the American Heart Association. 4(9), e002159

Portero V, Le Scouarnec S, Es-Salah-Lamoureux Z, Burel S, Gourraud JB, Bonnaud S, Lindenbaum P, Simonet F, Violleau J, Baron E, Moreau E, Scott C, Chatel S, Loussouarn G, O?Hara T, Mabo P, Dina C, Le Marec H, Schott JJ, Probst V, Baró I, Marionneau C, Charpentier F, Redon R. (2016). Dysfunction of the voltage-gated K+ channel beta-2 subunit in a familial case of Brugada syndrome., Journal of the American Heart Association. 5(6), e003122

Malak OA, Es-Salah-Lamoureux Z, Loussouarn G. (2017). hERG S4-S5 linker acts as a voltage-dependent ligand that binds to the activation gate and locks it in a closed state., Scientific Reports. 7(1), 113

Derangeon M, Montnach J, Cerpa CO, Jagu B, Patin J, Toumaniantz G, Girardeau A, Huang CLH, Colledge WH, Grace AA, Baró I, Charpentier F. (2017). Transforming growth factor ? receptor inhibition prevents ventricular fibrosis in a mouse model of progressive cardiac conduction disease., Cardiovascular Research. 113(5), 464-74

Burel S, Coyan FC, Lorenzini M, Meyer MR, Lichti CF, Brown JH, Loussouarn G, Charpentier F, Nerbonne JM, Townsend RR, Maier LS, Marionneau C. (2017). C-terminal phosphorylation of Na(V)1.5 impairs FGF13-dependent regulation of channel inactivation., Journal of Biological Chemistry. 292(42), 17431-48

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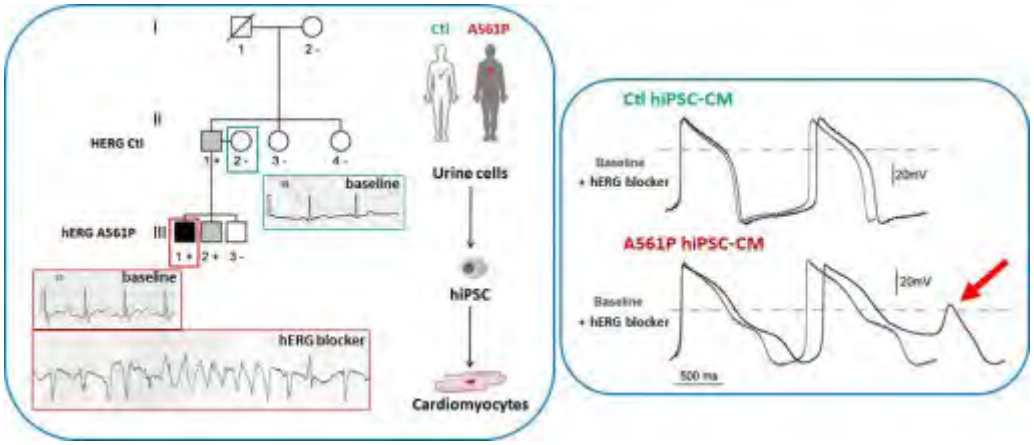
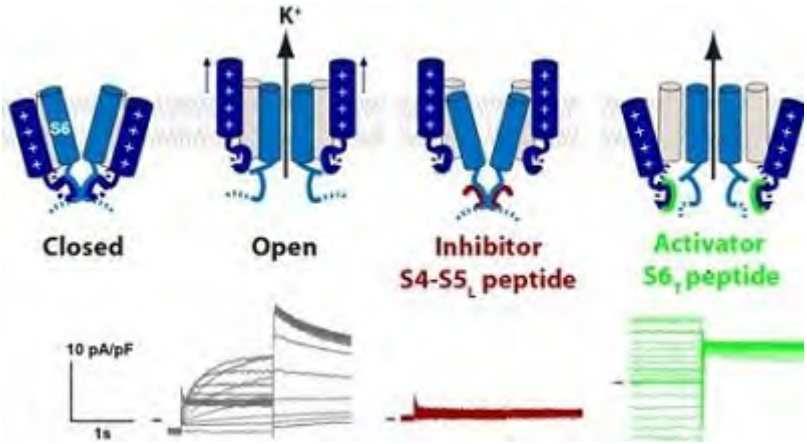
Phenotype of cardiomyocytes derived from iPS cells of a patient with type 2 long QT syndrome



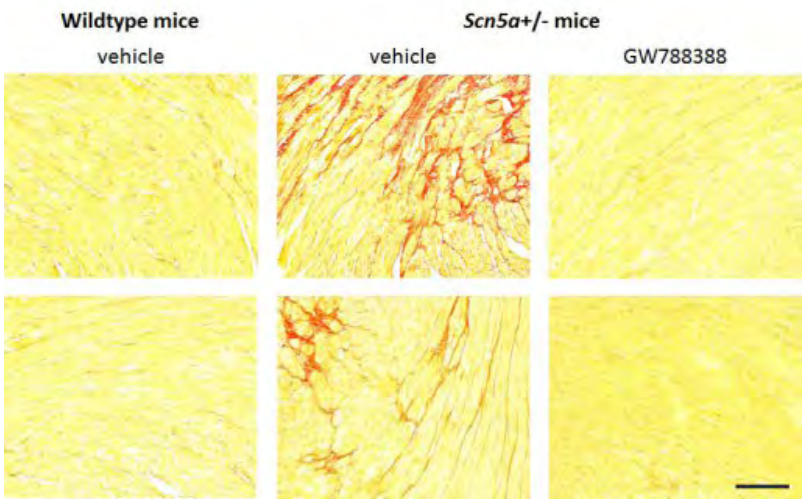
Action potentials (right panel) recorded in cardiomyocytes differentiated from induced pluripotent stem cells (hiPSC-CM) derived from urine cells of a patient with type 2 QT syndrome (p.A561P mutation of hERG channel) and his healthy mother (Ctl). Action potentials in A561P hiPSC-CM were longer than control ones. A hERG channel blocker induced ventricular arrhythmias in the patient and early afterdepolarizations (red arrow) in the patient's hiPSC-CMs.

Coupling mechanism between voltage sensors and the gate in the voltage-gated potassium channel hERG



hERG is formed by a tetrameric pore (S5-S6) surrounded by 4 voltage sensor domains (S1-S4). Covalently binding a peptide mimicking the S4-S5 linker (S4-S5L) to the channel S6 C-terminus (S6T) inhibits hERG. Conversely, covalently binding a peptide mimicking S6T to S4-S5L renders the channel voltage-independent. We thus show that S4-S5L acts as a voltage-controlled ligand that binds S6T to lock the channel in a closed state, elucidating the coupling between voltage sensors and the gate in hERG.

Inhibition of TGF-beta pathway prevents ageing-related fibrosis in heterozygous Scn5a knockout mice



Representative histological sections stained with picrosirius red from 60-week-old wildtype and heterozygous Scn5a knockout (Scn5a+/-) mice, a model of SCN5A-related progressive cardiac conduction disease, treated with either vehicle or GW788388, a blocker of TGF-? receptors, from the age of 45 weeks.

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Gervaise Loirand

Signaling in vascular and pulmonary pathophysiology

Université de Nantes
Inserm UMR 1087 CNRS UMR 6291
Richard Redon
Nantes

A specific strenght of the team is the strong interaction between basic scientists , interventional cardiologists/neurologists and vascular surgeons, and the close relationships between research and clinical departments allowing translational programs spanning from basic science to human disease.

Key facts

Team

- Researchers : 10
- Technicians : 6
- Postdoc fellows : 2
- PhD Students : 4

Translational approaches

- Patents : 4
- Clinical research grants : 2
- Industry partnerships : 1

Keywords

- G protein coupled receptor
- signal transduction
- intracranial aneurysm
- asthma
- hypertension
- airway
- artery
- smooth muscle
- pulmonary
- Cardiovascular
- contraction
- Rho proteins
- target discovery
- animal models
- functional exploration
- biochemistry
- molecular biology
- cell biology
- proteomics

Biological Resources

- - Animal models of vascular and pulmonary disease (hypertension, pulmonary hypertension, intracranial aneurysm, atherosclerosis, restenosis, asthma)
- - Ex vivo models of vascular and airway function analysis (arterial rings, bronchial ring, perfused kidney)
- - Primary culture (rodent en human bronchial and arterial vascular smooth muscle cells; human and rodent endothelial cells))
- - Original transgenic mice

Research Brief :

Our team projects are based on our previous work and acquired expertise on the small G proteins of the Rho family and their regulation in vascular smooth muscle cells and arterial diseases, but also more recently, in pulmonary pathologies. Our projetc relies on four main research programmes:
1. Regulation of RhoA activity: arterial pathologies and remodelling associated with aging (G. Loirand). This program particularly focus on the RhoA exchange factor, Arhgef1, identified as a target of interest in hypertension, and in the regulation of RhoA by phosphorylation
2. Role of Rac1 in arterial and bronchial smooth muscle cells (V. Sauzeau). The main objective is (i) to understand how Rac1 controls the contraction of bronchial smooth muscle cells, (ii) to define the mechanisms responsible for the activation of Rac1 in asthma, and (iii) to develop Rac1 inhibitors.
3. Physiopathology of intracranial aneurysms (G. Loirand). Based on our collaboration with the genetic team and the identification of rare causal variants in humans, our objective is to understand the pathophysiological mechanisms of intracranial aneurysms, through the development of relevant cellular and animal experimental models.
4. Inflammation/bronchial hyperreactivity relationship (A. Magnan). Particular interest is given to the relationship between Rac1/inflammation/contraction in asthma and to the confirmation of these pathways in the human pathology.

- **Methodologies Used :**

- Cell culture, cell biology
- Gene/function analysis (molecular biology, transfection, mutagenesis)
- Protein expression and function analysis, proteomics
- Animal models of human vascular and pulmonary diseases
- Transgenic mice, functional exploration (cardiovascular, pulmonary and metabolic)
- Ex vivo vascular and airway function analyses
- Imaging
- Target discovery
- Pharmacological screening

Publications

Guilluy C, Bregeon J, Toumaniantz G, Rolli-Derkinderen M, Retailleau K, Loufrani L, Henrion D, Scalbert E, Bril A, Torres RM (2010). The Rho exchange factor Arhgef1 mediates the effects of angiotensin II on vascular tone and blood pressure, Nat Med.. 16(2), 183-190

Loirand G, Sauzeau V, Pacaud P (2013). Small G proteins in the cardiovascular system: Physiological and pathological aspects., Physiol Rev.. 93(4), 1659-1720

Carbone ML, Brégeon J, Devos N, Chadeuf G, Blanchard A, Azizi, Pacaud P, Jeunemaître X, Loirand G. (2015). Ang II activates the RhoA exchange factor Arhgef1 in humans, Hypertension. 65(6), 1273-1278

Carbone ML, Chadeuf G, Heurtebise-Chétien S, Prieur X, Quillard T, Goueffic Y, Vaillant N, Rio M, Castan L, Durand M, Menguy C, Aureille J, Desfrançois J, Tesse A, Torres R, Loirand G. (2017). Leukocyte RhoA exchange factor Arhgef1 mediates vascular inflammation and atherosclerosis, J Clin Invest.. 127(12), 4516-4526

André-Grégoire G, Dilasser F, Chesné J, Braza F, Magnan A, Loirand G, Sauzeau V*. (2018). André-Grégoire G, Dilasser F, Chesné J,Targeting of Rac1 prevents bronchoconstriction and airway hyperresponsiveness, J Allergy Clin Immunol,.. (), In Press*

Bourcier R, Le Scouarnec S, Bonnaud, S, the ICAN Study Grp, Loirand G, Desal H*, Redon R* (2018). Rare coding variants in ANGPTL6 are associated with familial forms of intracranial aneurysm, Am J Hum Genet.. 102(1), 133-141*

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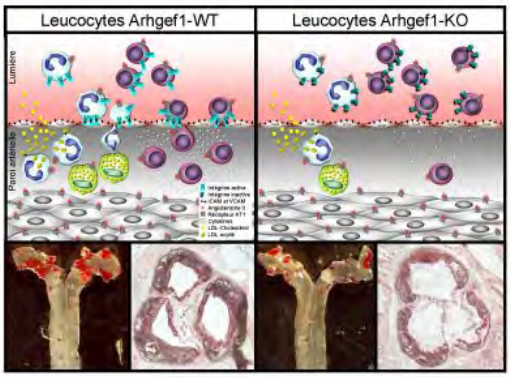
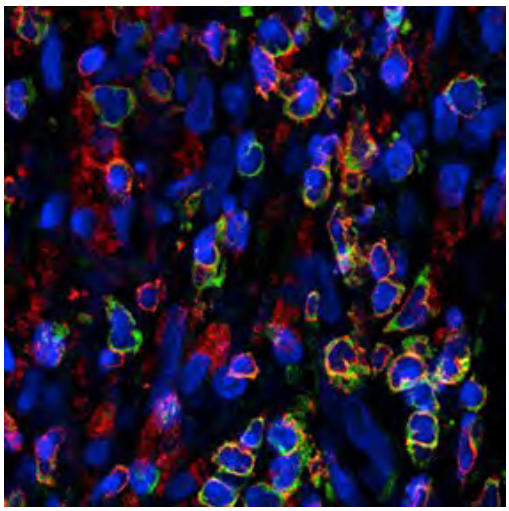
Arghef1 deletion limits atherosclerosis.



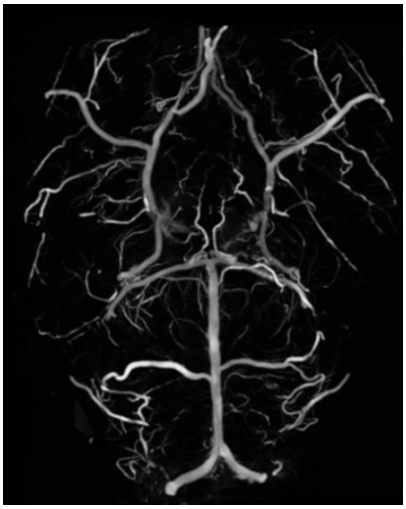
Atherosclerotic plaque formation is initiated by the penetration of LDL-cholesterol into the subendothelium and its oxidation which activates the endothelium and induces the expression of the adhesion molecules ICAM and VCAM. The stimulation of leukocytes (monocytes:light blue; T lymphocytes: violet) by Ang II/AT1 receptors activates Arhgef1, which induces the change in conformation of leukocyte integrins (left), high affinity for ICAM and VCAM, binding of leukocytes and their penetration.

Arghef1 expression in human atherosclerotic plaque



Immunostaining of cross section of human atherosclerotic carotid showing Arhgef1 expression in T cells in atherosclerotic lesion (CD3 red; Arhgef1 green).

Mouse cerebral vasculature



Micro-CT image of mouse (C57bl6) cerebral vasculature

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C2VN Marseille Center for CardioVascular and Nutrition research

Françoise Dignat-George
Christophe Dubois

Endothelium, blood cells and vascular diseases

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INRA 1260 INSERM 1263
ALESSI Marie-Christine
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Dysregulation of vascular homeostasis is a critical determinant of cardiovascular diseases. From mechanistic studies to translational and clinical research, our objective is to identify new molecular and cellular targets to improve diagnosis and therapy of vascular disorders.

Key facts

Team

• Researchers : 18
• Technicians : 10
• Postdoc fellows : 2
• PhD Students : 12

Translational approaches

• Patents : 6
• Clinical research grants : 20
• Industry partnerships : 4

International research links

• PhD program (TICARDIO) between C2VN, University of Mainz (Germany) and Maastricht (Netherlands)
• Pr Nigel Mackman, University of North Carolina, Chapel Hill, USA : Roles of TF-bearing microparticles in thrombosis associated with cancer (on going collaboration with a MTA)
• Rienk Nieuwland, Academic Medical Center, Laboratory of Experimental Clinical Chemistry (Vesicular Observation Center), Amsterdam, The Netherlands : "Microparticle standardization by flow cytometry"

Keywords

• Endothelial cells
• Vascular regeneration
• Vascular biology
• Thrombosis
• Microparticles
• Experimental animal models
• Vessels imaging
• Molecular and cellular biology
• Intravital microscopy
• Angiogenesis models

Biological Resources

• In vivo models of thrombosis
• Vascular disease patients cohorts
• Animal models of ischemia
• Trangenic mouse
• Biobanks of patient-derived endothelial cells

Research Brief :

The dynamic interplay between endothelium cells and molecular and cellular and subcellular blood components is a key component of vascular homeostasis. Their dysregulations are at the crossroad of pathogenic processes underlying vascular thrombotic, inflammatory or ischemic diseases. Better knowledge of the molecular pathways and cellular effectors of these processes is challenging to develop biomarkers and therapeutic options targeting cardiovascular risk. Our research aims at addressing the contribution of leucocytes, endothelial progenitors, extracellular vesicles and Nets in immuno-thrombosis, vascular injury and regeneration. Based on original in vitro and in vivo models our goal is to transpose this knowledge to clinical practice through delineation of original biomarkers, imaging strategies and cell-based therapies allowing to promote a personalized approach of vascular medicine. Main topics include 1/ Understanding of the interactions of neutrophils platelets and nets at with endothelium and their contribution to thrombosis and cancer. 2/ Characterization of the structure-function relationship of extracellular vesicles that determine their role in the coagulolytic balance and their significance in vascular diseases 3/ Study of the progenitor cells-dependent endothelial repair processes in vascular diseases, and identification of innovative imaging strategies and cell-based therapies with clinical usefulness in ischemic vasculopathies.

• **Methodologies Used :**

Molecular and cellular biology
Vascular cell culture
Vessels functional imaging
Angiogenesis models
Animals models of thrombosis
Intravital microscopy

Publications

Berda-Haddad Y, Robert S, Salers P, Zekraoui L, Farnarier C, Dinarello CA, Dignat-George F, Kaplanski G. (2011). Sterile inflammation of endothelial cell-derived apoptotic bodies is mediated by interleukin-1?., Proc Natl Acad Sci. 108(51), 20684-9

Darbousset R, Thomas GM, Mezouar S, Frère C, Bonier R, Mackman N, Renné T, Dignat-George F, Dubois C, Panicot-Dubois L. (2012). Tissue factor-positive neutrophils bind to injured endothelial wall and initiate thrombus formation., Blood. 120(10), 2133-43

Darbousset R, Delierneux C, Mezouar S, Hego A, Lecut C, Guillaumat I, Riederer MA, Evans RJ, Dignat-George F, Panicot-Dubois L, Oury C, Dubois C. (2014). P2X1 expressed on polymorphonuclear neutrophils and platelets is required for thrombosis in mice., Blood. 124(16), 2575-85

Vassallo PF, Simoncini S, Ligi I, Chateau AL, Bachelier R, Robert S, Morere J, Fernandez S, Guillet B, Marcelli M, Tellier E, Pascal A, Simeoni U, Anfosso F, Magdinier F, Dignat-George F, Sabatier F. (2014). Accelerated senescence of cord blood endothelial progenitor cells in premature neonates is driven by SIRT1 decreased expression., Blood. 123(13), 2116-26

Todorova D, Simoncini S, Lacroix R, Sabatier F, Dignat-George F. (2017). Extracellular Vesicles in Angiogenesis., Circ Res.. 120(10), 1658-1673

Paul P, Picard C, Sampol E, Lyonnet L, Di Cristofaro J, Paul-Delvaux L, Lano G, Nicolino-Brunet C, Ravis E, Collart F, Dignat-George F, Dussol B, Sabatier F, Mouly-Bandini A. (2018). Genetic and Functional Profiling of CD16-Dependent Natural Killer Activation Identifies Patients at Higher Risk of Cardiac Allograft Vasculopathy., Circulation. 137(10), 1049-1059

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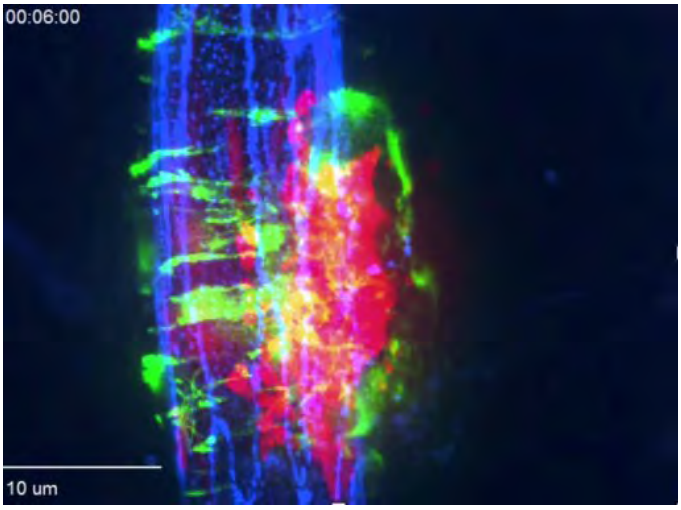
Research topic and strategy

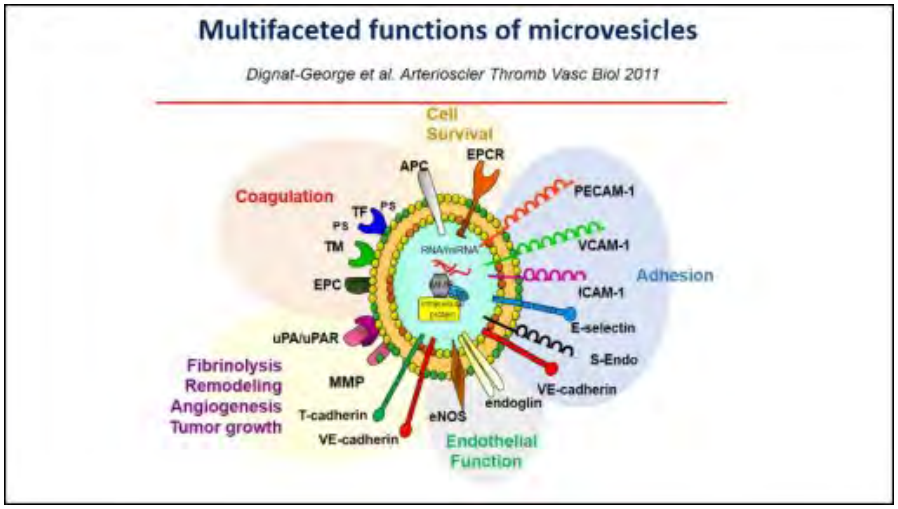
Our research strategy is focused on the mechanisms by which the endothelium dynamically interacts with its environment and their dysregulation in vascular disorders. From this basic knowledge we aim to identify new pathways and targets towards an innovative and personalized vascular médicine.

Real-time observation of a growing thrombus in a living mouse



A laser-induced injury was performed on arterioles of a living mouse leading to the activation of the endothelium (blue), the accumulation of platelets (red) at the site of injury and the generation of fibrin (depicted in green). Platelets, endothelial cells and fibrin were observed by real-time confocal intravital microscopy.

Microparticles



Endothelial microparticles are considered as a miniature version of endothelial cells. They express a large repertoire of endothelial molecules and biological functions that are related to their involment in the tuning of vascular homeostasis.

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C2VN Marseille
Center for CardioVascular and Nutrition research

Régis Guieu

Dysoxia, purinergic system and inflammation

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Marie-Christine Alessi
Marseille

Our team is the only one who have developped specific Tools for the identification of spare adenosine receptors and complete assessment of adenosinergic profile in the area of cardiovascular disease.

Key facts

Team

- Researchers : 18
- Technicians : 6
- Postdoc fellows : 0
- PhD Students : 5

Translational approaches

- Patents : 2
- Clinical research grants : 2
- Industry partnerships : 2

International research links

- USA and Sweden
- Italy and Belgium
- Spain and Denmark

Keywords

- Coronary artery disease
- Arrhythmia
- Biomarkers
- Adenosinergic system
- Dysoxia
- Cell culture
- Animals models
- Antibodies
- Clinical research

Biological Resources

- Transgenic cells
- Animal models (mice and rat)
- Cohorts of patients

Research Brief :

The expertise of the team concern the role of the adenosinergic system (including adenosine metabolism, receptors and CD26/DPPIV system (see figure 1) in the control of the cardiovascular system during dysoxia, ischemia or inflammation (see figures 2,3). We focused on the role of this system and of drugs that modulate adenosine metabolism in the area of hypoxia, ischemia, coronary blood flow and arrhythmia. We identified new biomarkers of ischemia, heart failure and arrhythmia. We identified : I) the role of the adenosinergic system in the occurrence of neurocardiogenic syncope and in atrial fibrillation; II) a specific pharmacological profile associated with coronary artery disease; III) We shown that lymphocyte is a good model for the study of adenosinergic system in the cardiovascular apparatus; IV) We reported that H2S which his produced from HCy catabolism via the trans-sulfuration pathway, down-regulates A2AR expression in hypoxic conditions via repression of the NF-kB. This indicates that HCy constitutes a risk factor in cardiovascular disease by lowering the adenosinergic T-cell immunosuppression, which, in turn, sustains the inflammatory process; V) We aim to evaluate the influence of extreme oxygenation on the cardiovascular system of animals and cell culture, using special hypoxia chambers for animals. The hyperbaric platform, is unique in Europe. This expertise has been developed in the analysis of cardiovascular response to hypoxia, hyperoxia and/or hyperbaria.

- **Methodologies Used :**

Cell culture animal models.
Hyperbaria chamber, chemical and physical model of hypoxia.
Clinical research.

Publications

Bonello L, Laine M, Kipson N, Mancini J, Helal O, Fromonot J, Gariboldi V, Condo J, Thuny F, Frere C, Camoin-Jau L, Paganelli F, Dignat-George F, Guieu R. (2014). Ticagrelor increases adenosine plasma concentration in patients with an acute coronary syndrome., JACC. 63(9), 872-877

Bruzzese L, Rostain JC, Née L, Condo J, Mottola G, Adjriou N, Mercier L, Berge-Lefranc JL, Fromonot J, Kipson N, Lucciano M, Durand-Gorde JM, Jammes Y, Guieu R, Ruf J, Fenouillet E. (2015). Effect of hyperoxic and hyperbaric conditions on the adenosinergic pathway and CD26 expression in rat., J Appl Physiol. 119(2), 140-147

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Gariboldi V, Vairo D, Guieu R, Marlingue M, Ravis E, Lagier D, Mari A, Thery E, Collart F, Gaudry M, Bonello L, Paganelli F, Condo J, Kipson N, Fenouillet E, Ruf J, Mottola G. (2017). Expressions of adenosine A(2A) receptors in coronary arteries and peripheral blood mononuclear cells are correlated in coronary artery disease patients, Int J Cardiol. 230(), 427-431

-Paganelli F, Resseguier N, Marlinge M, Laine M, Malergue F, Kipson N, ArmangauP, Pezzoli N, Kerbaul F, Bonello L, Mottola G, Fenouillet E, Guieu R, Ruf J. (2018). Receptor Predicts Reduced Fractional Flow Reserve in Patients With Suspected Coronary Artery Disease., J Am Heart Assoc. 7(8), 1-11

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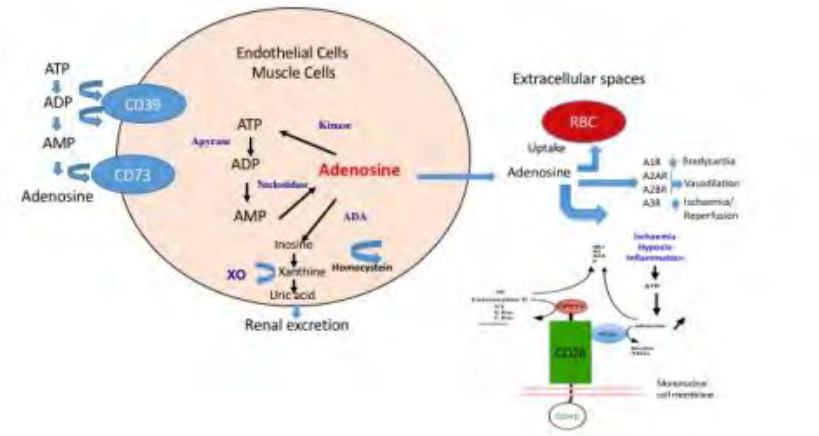
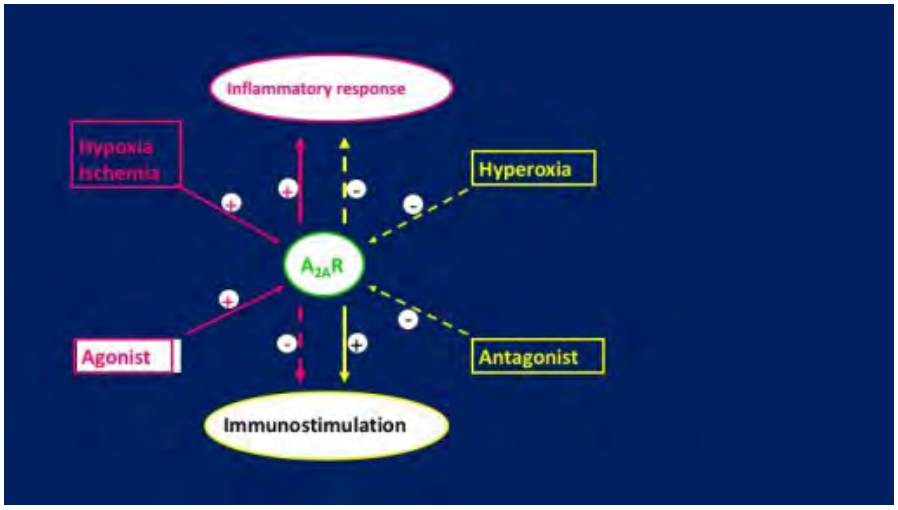
Simplified representation of the adenosinergic system



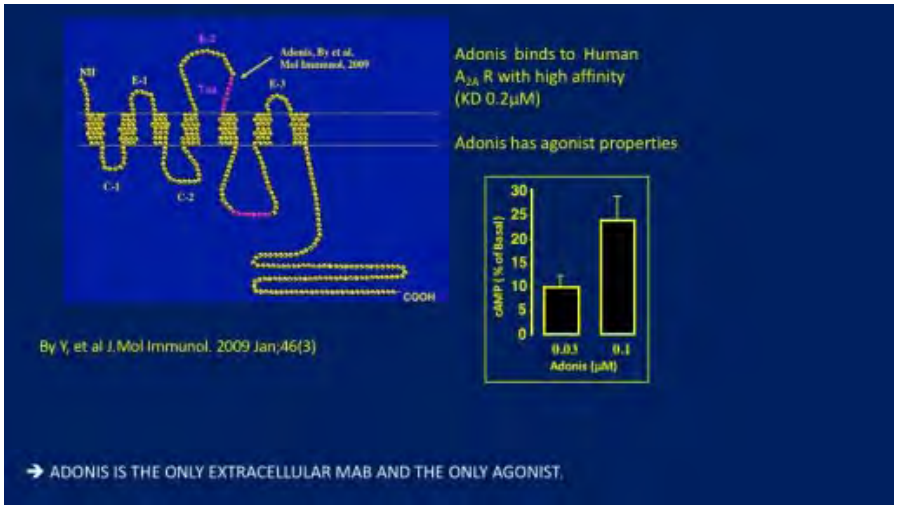
Simplified representation of the adenosinergic system and of its implication in the control of the cardiovascular system

A2A receptor and hypoxia



Simplified representation of the role of the A2A adenosine receptors on hypoxia-induced inflammation

Adonis



Adonis a unique anti A2A adenosine receptor antibody with agonist properties, that permit to evaluate the pharmacological profile of patients suffering from arrhythmia or coronary artery disease

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C2VN Marseille
Center for CardioVascular and Nutrition research

Stéphane BURTEY
Marcel BLOT-CHABAUD

New endothelial molecular targets (NEMOT)

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Marie-Christine Alessi
Marseille

This team identified two new endothelial molecules involved in inflammation, thrombosis and angiogenesis (aryl hydrocarbon receptor and CD146) with the objective of using them in personnalized medicine as biomarkers and therapeutic targets

Key facts

Team

- Researchers : 11
- Technicians : 4
- Postdoc fellows : 1
- PhD Students : 6

Translational approaches

- Patents : 5
- Clinical research grants : 4
- Industry partnerships : 2

International research links

- Belgium
- USA

Keywords

- CD146
- Cancer
- Chronic kidney disease
- Endothelium
- Uremic toxins
- Cellular biology/cytometry
- Molecular biology
- Translational medecine
- flow culture
- Animals models

Biological Resources

- Ahr KO mouse
- Antibodies against CD146 and recombinant CD146 proteins
- EVITHUP cohort
- Flow culture of endothelial cells
- CD146 KO mice
- Binational cohorts of hemodialysed patients (France/Algeria)

Research Brief :

The goal of the "New Endothelial Molecular Targets" team is to investigate two endothelial proteins identified by our group as new potential vascular therapeutic targets involved in inflammation, angiogenesis and atherothrombosis: the aryl hydrocarbon receptor (AhR) and CD146. AhR is a receptor for numerous solutes, including uremic toxins of indole family, and its activation in EC is associated with a procoagulant and proinflammatory phenotype leading to atherothrombosis. AHR plays a key role in the expression of PgP in the liver in response to uremic toxins. CD146 is a transmembrane glycoprotein belonging to the Ig superfamily, also detectable in the bloodstream as a soluble form (sCD146).The CD146/sCD146 system is expressed on both EC, where it is involved in angiogenesis and inflammation, and numerous tumor cells, where it induces tumor angiogenesis and growth.
The team IV project will combine the knowledge and know-how of two research groups sharing expertise in the original endothelial target identified by VRCM.
Our objectives for the next five years are 1/ to characterize the functions of these proteins in endothelial cells, 2/ to further elucidate their interrelationships and 3/ to validate them as targets in vascular diseases in relevant preclinical models, such as flow cell culture and "close-to-disease" mouse models, in order to generate innovative devices for diagnostic or therapeutic applications.

- **Methodologies Used :**

Mouse models, Flow culture, in vivo video microscopy, molecular biology.

Publications

Gondouin B, Cerini C, Dou L, Sallée M, Duval-Sabatier A, Pletinck A, Calaf R, Lacroix R, Jourde-Chiche N, Poitevin S, Arnaud L, Vanholder R, Brunet P, Dignat-George F, Burtey S (2013). Indolic uremic solutes increase tissue factor production in endothelial cells by the aryl hydrocarbon receptor pathway, Kidney Int. 84(4), 733

Dou L1, Sallée M2, Cerini C3, Poitevin S3, Gondouin B2, Jourde-Chiche N4, Fallague K3, Brunet P2, Calaf R5, Dussol B2, Mallet B6, Dignat-George F3, Burtey S2 (2015). The cardiovascular effect of the uremic solute indole-3 acetic acid, J Am Soc Nephrol. 26(4), 876

Satlin, Nollet, Garigue, Fernadez, Vivancos, Essaadi, Muller, bachelier, Foucault-Bertaud, Fugazza, Leroyer, Bardin, Guillet, Dignat-George, Blot-Chabaud (2016). Targeting soluble CD146 with a neutralizing antibody inhibits vascularization, growth and survival of CD146-positive tumors, Oncogene. 35(), 5489-5500

Kaspi, Heim, Granel, Guillet, Stalin, Nollet, Foucault-Bertaud, Robaglia-Schlupp, Roll, Cau, Leroyer, Bachelier, Benyamine, Dignat-George, Blot-Chabaud, Bardin (2017). Identification of CD146as a novel molecular actor involved in systemic sclerosis, J Allergy Clin Immunol. 140(5), 1448-1451

Dou L, Poitevin S, Sallée M, Addi T, Gondouin B, McKay N, Denison MS, Jourde-Chiche N, Duval-Sabatier A, Cerini C, Brunet P, Dignat-George F, Burtey S (2018). Aryl hydrocarbon receptor is activated in patients and mice with chronic kidney disease, Kidney Int. 93(4), 986

Dufies, Nollet, Ambrossetti, Traboulsi, Viotti, Borchiellini, Grepin, Parola, Helley-Rusick, Bensalah, Ravaud, Bernhard, Schiappa, Bardin, Dignat-George, Rioux-Leclercq, Oudard, Négrier, Ferrero, Chamorey, Pages, Blot-Chabaud* (2018). Soluble CD146 is a predictive marker of pejorative evolution and of sunitinib efficacy in clear cell renal carcinoma, Theranostics. 8(9), 2447-2458*

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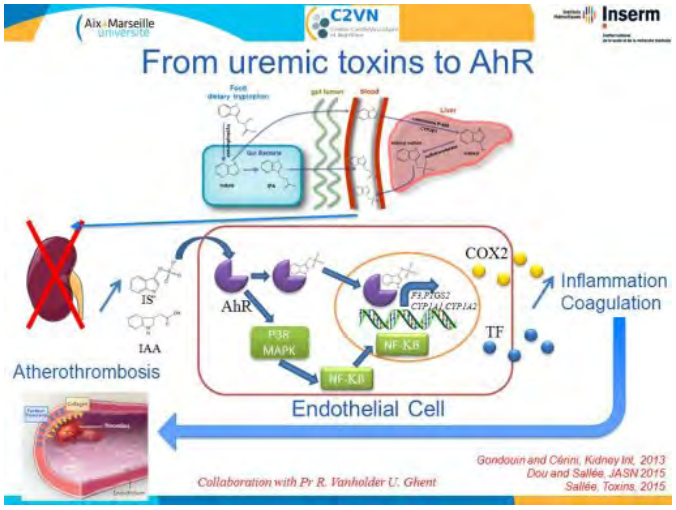
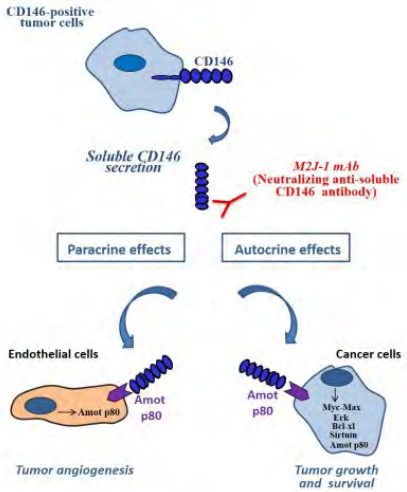
From uremic toxins to Atherothrombosis



Indoles (indoxyl sulfate and indole acetic acid) are uremic toxins derived from the tryptophan metabolism in the gut. They activate aryl hydrocarbon receptor in the endothelial cells. AhR activation induces endothelial dysfunction leading to inflammation and procoagulant profil. Endothelial dysfunction, mainly expression of Tissue Factor, could lead to atherothrombosis and explains the increased cardiovascular mortality observed during Chronic kidney disease.

Summary of the effects induced by soluble CD146 on cancer cells



CD146-positive tumors secrete soluble CD146 through shedding of the membrane form. This soluble CD146 generates both paracrine and autocrine effects trough binding to angiomotin. Paracrine effects involves proliferation of endothelial cells , leading to tumor angiogenesis. Autocrine effects are mediated through the induction of different factors in cancer cells, leading to tumor growth and survival.
All these effects can be antagonized by the neutralizing anti-soluble CD146 M2J-1 antibody.

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C2VN Marseille
Center for CardioVascular and Nutrition research

Marie-Christine Alessi
Pierre Emmanuel Morange

Thrombosis, platelets and vascular disorders

Aix-Marseille Université
INRA UMR 1260 INSERM UMR 1263
Marie-Christine Alessi
Marseille

Thrombosis is a major clinical problem. Through the study of large populations and rare diseases we aim to identify hereditary and non-hereditary components that contribute to haemostasis and thrombosis. Our major goal is to identify relevant biomarkers and new therapeutical targets.

Key facts

Team

- Researchers : 17
- Technicians : 18
- Postdoc fellows : 3
- PhD Students : 10

Translational approaches

- Patents : 3
- Clinical research grants : 2
- Industry partnerships : 5

International research links

- Ashford MLJ university of Dundee (UK)
- Panteleev M University of Moscow
- PhD Program (TICARDIO) between C2VN, university of mainz (germany) and Maastricht (Netherlands)

Keywords

- Thrombosis
- Haemostasis
- Platelets
- Cardiovascular
- Pathophysiology
- Biomarkers
- Adipose tissue
- Genome editing
- Cell culture

Biological Resources

- Animal models (mice and rat)
- Cohorts of patients (thrombosis) and families (rare haemostasis disease)
- Main laboratory cell lines
- Biobank (accredited biological resource center, Hemovasc)

Research Brief :

The formation of thrombi at sites of vessel lesions is a major clinical problem. Thrombosis results from the interaction of genetic and environmental risk factors. Progress in this field requires the identification of specific hereditary and environmental risk factors in affected individuals and of the design of new antithrombotic therapies. Emerging technologies are beginning to allow the unbiased characterization of variation in genes, RNA, proteins and metabolites associated with thrombotic conditions. These approaches will lead us to identify genes, epigenetic and metabolites variations that could be biomarkers themselves or will point to circulating markers of thrombosis for further exploration. Furthermore, by studying rare inherited diseases causing platelet dysfunction or low platelet counts, we aim to identify new pathways involved in thrombosis. We extend our objectives to environmental factors through the understanding of the role of platelets in tissue injury in various pathological contexts, such as viral infection. We also examine how nutrition and obesity can affect thrombosis and the cardiovascular pathophysiology. During obesity, expansion of ectopic fat (epicardial and perivascular depots) may exert adverse lipotoxic, prothrombotic, and proinflammatory effects. Using noninvasive imaging we will unveil the direct myocardial and vascular targets of ectopic adipose tissue action.

• Methodologies Used :

Cohort evaluation / Genotyping plateforms
genome editing
Magnetic Resonance Imaging (collaborative work)
Rat model of metabolic syndrome / Murine models of thrombosis and obesity
Cell cultures, flow chamber, microscopy
Biological evaluation (cytometry, qPCR, cell culture...)

Publications

Rocanin-Arjo A, Cohen W, Carcaillon L, Frère C, Saut N, Letenneur L, Alhenc-Gelas M, Dupuy AM, Bertrand M, Alessi MC, Germain M, Wild PS, Zeller T, Cambien F, Goodall AH, Amouyel P, Scarabin PY, Trégouët DA, Morange PE (2014). A meta-analysis of genome-wide association studies identifies ORM1 as a novel gene controlling thrombin generation potential, Blood. 123(5), 777-785

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Germain M, Chasman DI, de Haan H, Tang W, Lindström S, Weng LC, de Andrade M, de Visser MC, Wiggins KL, Suchon P, Saut N, Smadja DM, Le Gal G, van Hylckama Vlieg A, Di Narzo A, Hao K, Nelson CP, Rocanin-Arjo A, Folkersen L, Monajemi R, Rose LM, Brody JA, Slagboom E, Aïssi D, Gagnon F, Deleuze JF, Deloukas P, Tzourio C, Dartigues JF, Berr C, Taylor KD, Civelek M, Eriksson P; Cardiogenics Consortium, Psaty BM, Houwing-Duitermaat J, Goodall AH, Cambien F, Kraft P, Amouyel P, Samani NJ, Basu S, Ridker PM, Rosendaal FR, Kabrhel C, Folsom AR, Heit J, Reitsma PH, Trégouët DA, Smith NL, Morange PE (2015). Meta-analysis of 65,734 individuals identifies TSPAN15 and SLC44A2 as two susceptibility loci for venous thromboembolism, Am J Hum Genet. 96(4), 532-542

Cuisset T, Deharo P, Quilici J, Johnson TW, Deffarges S, Bassez C, Bonnet G, Fourcade L, Mouret JP, Lambert M, Verdier V, Morange PE, Alessi MC, Bonnet JL. (2017). Benefit of switching dual antiplatelet therapy after acute coronary syndrome: the TOPIC (timing of platelet inhibition after acute coronary syndrome) randomized study. Eur Heart J., Eur Heart J. 38(41), 3070-3078

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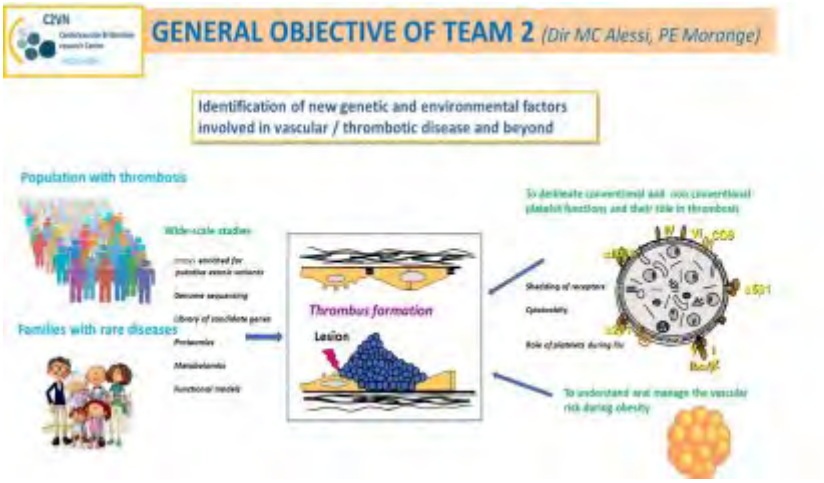

Main objectives of team 2 of the C2VN

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Patrick Lacolley

Hypercoagulability, arterial stiffness and ageing

Université de Lorraine
Inserm U1116
Patrick Lacolley
Vandoeuvre-les-Nancy

Interaction and integration of basic and clinical research in the cardiovascular biology field based on the combination of expertises on vascular stiffness, coagulation and original imaging tools

Key facts

Team

- Researchers : 12
- Technicians : 6
- Postdoc fellows : 4
- PhD Students : 5

Translational approaches

- Patents : 0
- Clinical research grants : 6
- Industry partnerships : 1

International research links

- Europe
- United States
- Australia

Keywords

- Vascular smooth muscle cells
- Ageing
- Arterial stiffness
- Hypercoagulability
- Telomere
- MicroPET
- Vascular echotracking
- Isolated vessels
- Thrombin generation assay
- Telomere measurement

Biological Resources

- cardiovascular tissues and blood samples from humans (aortic aneuryms), rat and mouse models
- validated cohorts (antiphospholipid, heart failure, elderly, post-menopausal women, systolic hypertension)

Research Brief :

The team aims at deciphering vascular stiffening and hypercoagulable phenotypes as well telomere dynamics and inflammation in arterial ageing. It has combined three approaches, knockout murine models to inactivate genes coding for molecular targets, in vitro perfused arterial segments, and cell cultures to show that vascular smooth muscle cells and integrins are key players in mechanotransduction and arterial stiffness, thrombin generation within the vessel wall and vascular mechanisms of ageing. The translational strategy has focused on the characterization of arterial ageing phenotypes, providing an improved understanding of the connections between the vessel wall and thrombin generation, and the selection of biomarkers for cardiovascular pathologies.

Our research on the process of early vascular ageing has generated basic work highlighting the major role of vascular smooth muscle cell (VSMC) plasticity in arterial stiffening and thrombosis. Our work has contributed to identifying new molecular mechanisms of arterial stiffening and its complications such as dissection, aneurysm and fibrosis of the vascular wall as well as atherothrombosis.

The project on mechanotransduction is supported by the EU community (FEDER).

Methodologies Used :

Methods to measure parameters of arterial stiffness and thrombin generation in vivo and in vitro: echotracking, pulse wave velocity, calibrated automated thrombography (whole blood, plasma)
Appropriate animal models (pharmacology, transgenic)
Primary cultures of human, rat and mouse vascular smooth muscle cells (cyclic stretch, siRNA, confocal and second harmonic generation microscopy)
Flow cytometry for extracellular vesicles, calcium and cell phenotypic markers
Telomere length measurement (Southern blots of the terminal restriction fragments)
Single photon emission computed tomography and hybrid imaging with X-ray computed tomography and 18F-fluorodeoxyglucose positron emission tomography
Cohorts, pharmacological trials, genetics

Publications

Zuily S, Regnault V, Selton-Suty C, Eschwège V, Bruntz JF, Bode-Dotto E, De Maistre E, Dotto P, Perret-Guillaume C, Lecompte T, Wahl D. (2011). Increased Risk for Heart Valve Disease Associated With Antiphospholipid Antibodies in Patients With Systemic Lupus Erythematosus: Meta-Analysis of Echocardiographic Studies.., CIRCULATION. 124(), 215-224

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Lagrange J, Li Z, Fassot C, Bourhim M, Louis H, Nguyen Dinh Cat A, Parlakian A, Wahl D, Lacolley P, Jaisser F, Regnault V. (2014). Endothelial mineralocorticoid receptor activation enhances endothelial protein C receptor and decreases vascular thrombosis in mice., FASEB JOURNAL. 28(), 2062-2072

Benetos A, Labat C, Rossignol P, Fay R, Rolland Y, Valbusa F, Salvi P, Zamboni M, Manckoundia P, Hanon O, Gautier S. (2015). Treatment with multiple blood pressure medications, achieved blood pressure, and mortality in older nursing home residents., JAMA INTERNAL MEDICINE. 175(), 989-995

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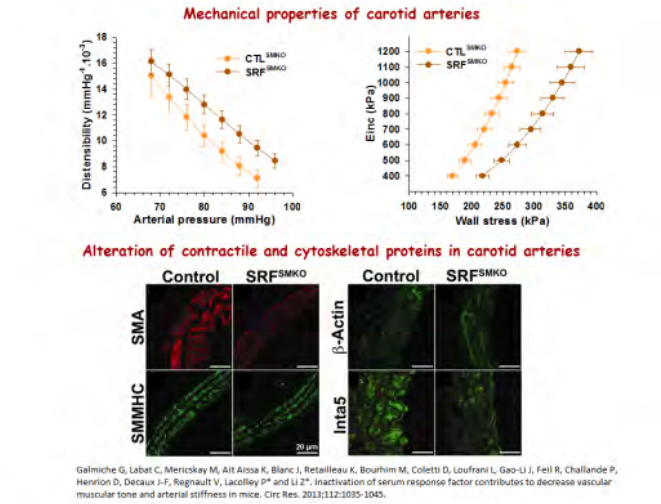
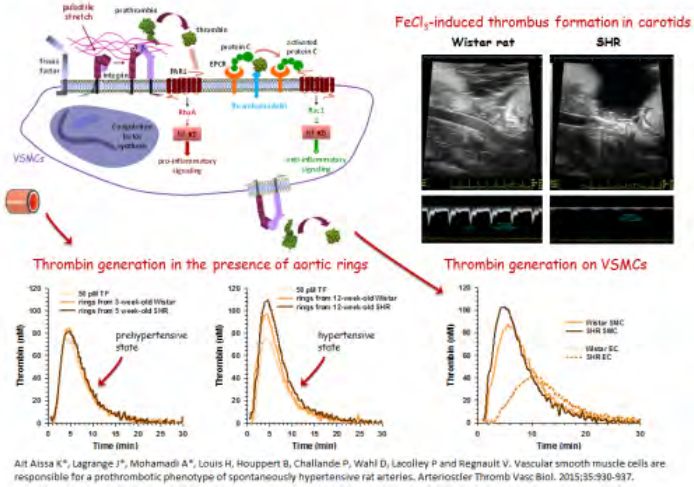
SRF-related decreases in contractile proteins and cell-ECM attachment increase arterial elasticity



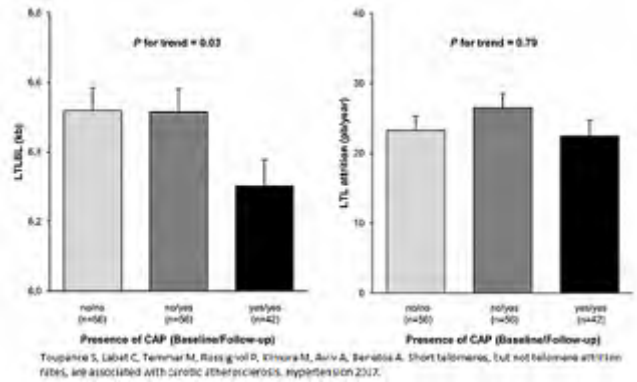
Top: mechanical properties of carotid arteries from control (CTLSMKO) and smooth muscle-specific knockout of serum response factor (SRFSMKO mice); distensibility?arterial pressure (AP) curves (left) and incremental elastic modulus (Einc)-wall stress (WS) curves (right). Bottom: Alteration of contractile and cytoskeletal proteins. Carotid sections stained with antibodies against smooth muscle alpha-actin (SMA; red) and myosin heavy chain (SM-MHC), beta-actin, alpha5 integrin (green).

Prothrombotic phenotype of spontaneously hypertensive rat arteries



Top right: FeCl3-induced thrombus formation in carotid arteries from 12-week-old spontaneously hypertensive rats (SHR) or Wistar rats. Bottom left: Thrombin generation curves in a Wistar platelet-free plasma pool triggered with 50 pmol/L tissue factor (TF) or with 2 mm rings from thoracic aortas of 5-week-old or 12-week-old SHR or Wistar. Bottom right: Thrombin generation curves at the surfaces of vascular smooth muscle cells (VSMCs) or endothelial cells (ECs) from 12-week-old SHR or Wistar.

Baseline leukocyte telomere length and leukocyte telomere attrition versus atherosclerotic plaques



Adjusted baseline leukocyte telomere length (LTL) (kilo base pairs) versus the presence of carotid atherosclerotic plaque (CAP) at baseline (BL) and follow-up (left); Adjusted LTL attrition (base pair/year) versus the presence of CAP at baseline and follow-up (right). Values are mean ± SEM. No/no: absence of CAP in both BL and follow-up examinations; no/yes: presence of CAP only at the follow-up examination; yes/yes: presence of CAP in both BL and follow-up examinations.

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Saïd Bendahhou

Ion channels pathophysiology

Université Côte d'Azur
CNRS UMR7370
Jacques Barhanin
Nice

Key facts

Team

• Researchers : 1
• Technicians : 1
• Postdoc fellows : 1
• PhD Students : 2

Translational approaches

• Patents : 0
• Clinical research grants : 0
• Industry partnerships : 0

International research links

• USA
• Germany
• Italy

Keywords

• Ion channels
• Channelopathies
• Skeletal muscle
• Electrophysiology
• Microscopy
• Biochemistry

Biological Resources

• Human biopsies
• iPS cells
• Mammalian cell cuture

The team investigates the role of ion channels in non excitable tissues to shed lights on rare disorders.

• **Methodologies Used :**

- Electrophysiology
- Imaging
- iPS reprogramming and differentiation
- protein analysis
- Transcript analysis

Publications

Simkin D., Léna I., Landrieu P., Lion-François L., Sternberg D., Fontaine B., and Bendahhou S. (2011). Mechanisms underlying a life-threatening skeletal muscle Na+ channel disorder., J. Physiol. (Lond.). 589(3115), 3124

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Sacco S., Giuliano S., Sacconi S., Desnuelle C., Barhanin J., Amri E., and Bendahhou S. (2015). The inward rectifier potassium channel kir2.1 is required for osteoblastogenesis, Hum. Mol. Genet.. 24(471), 479

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Agnès VINET

LaPEC

University of Avignon
Equipe d'Accueil EA4278
Agnes VINET
Avignon

Translational approach (from human to molecular research) to study the effects of exercise and/or nutrition on cardiovascular dysfunctions in cardio-metabolic patients with focus on adipose tissue, inflammation and oxydative stress

Key facts

Team

• Researchers : 11
• Technicians : 1
• Postdoc fellows : 1
• PhD Students : 7

Translational approaches

• Patents : 0
• Clinical research grants : 2
• Industry partnerships : 4

International research links

• ACU Melbourne (Australia)
• Miguel Hernandez University (Elche, Spain)
• University of York (Toronto, Canada)

Keywords

• adipose tissue
• nutrition
• exercise
• cardiac function
• vascular function
• cell culture
• Cardiac and vascular ultrasonography
• isolated heart
• artery rings
• western blotting

Biological Resources

• Clinical experimental platform allowing the assessment of physical aptitude and the cardiovascular system
• Approved animal house (rodents)
• Animal experimentation platform allowing the assessment of the cardiovascular system and underlying cellular and molecular mechanisms

Research Brief :

The translational project of the Laboratoire de Pharm-Ecologie CardioVasculaire (LaPEC, EA4278) focusses on vascular and myocardial dysfunctions, with associated links to prevention and rehabilitation in cardiac-metabolic diseases through physical exercise and/or nutrition. The implication of the inflammatory status and the nitric oxide (NO) channel in the genesis of the oxidant stress is central to these projects. Specific focus is also addressed on the effect of adipose tissue, its different phenotype and localization, and its related inflammation and oxidative stress on cardiovascular function. The potential outcomes of our research fall within the scope of a better appraisal and therapeutic efficiency through:
- the identification of at risk populations at an early stage of vascular and myocardial dysfunction;
- the revelation of precursor signs impacted by exercise and/or nutrition, allowing better pharmacological targeting, working to the objective of synergetic and potentially additive effects. These actions ultimately support an overall public health approach which is also designed to limit costs linked to treating these pathologies.

• **Methodologies Used :**

- Resting and stressed (dobutamin or exercise) echocardiography in humans and animals (Vivid Q, GE and Vevo, VisualSonic)
- Resting and stressed (exercise) Vascular ultrasonography in humans and animals (Vivid Q, GE and Vevo, VisualSonic)
- Laser Doppler in humans and animals (Perisoft and Pericam, Perimed)
- Isolated heart (Langerdorf)
- Myocardial ischemia-reperfusion
- Isolated artery (aortic, mesenteric)
- Biochemical assays (Western blot analysis, immunohistochemistry, ELISA)
- Cell culture

Publications

J. Serrano-Ferrer, G. Walther, F. Dutheil, D. Courteix, B. Lesourd, R. Chapier, G. Naughton, A. Vinet, P. Obert (2014). Right ventricle mechanics in metabolic syndrome without type-2 diabetes: effects of a 3-month lifestyle intervention program. Cardiovascular, Cardiovascular Diabetology. 3(13), 116

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S. Dimassi, K. Chahed, S. Boumiza, M. Canault, Z. Tabka, P. Laurant, C. Riva. (2016). Role of eNOS and NOX-containing microparticles in endothelial dysfunction in patients with obesity., Obesity. 24(6), 1305-12

Kleindienst A, Battault S, Belaidi E, Tanguy S, Rosselin M, Boulghobra D, Meyer G, Gayrard S, Walther G, Geny B, Durand G, Cazorla O, Reboul C (2016). Exercise does not activate the beta-3 adrenergic receptor-eNOS pathway, but reduces inducible NOS expression to protect the heart of obese diabetic mice., Basic Res Cardiol.. 111(4), 40

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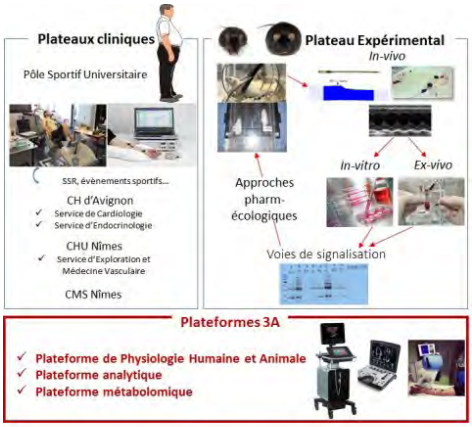
Translational approach in cardiometabolic disease



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Key facts

Team

- Researchers : 32
- Technicians : 8
- Postdoc fellows : 3
- PhD Students : 36

Translational approaches

- Patents : 2
- Clinical research grants : 12
- Industry partnerships : 2

International research links

- Belgique
- Angleterre
- Etats Unis

Keywords

- pulse pressure
- calcified aortic valve disease
- uraemia
- cardiovascular calcification
- bone remodelling
- molecular biology
- cardiovascular exploration
- bone cell evaluation
- animal model of chronic kidney disease

Biological Resources

- primary cell culture
- secondary cell culture
- wild type and knock-out mice
- biological samples (animal and human)

Said Kamel

Pathophysiological mechanisms and consequences of cardiovascular calcifications: role of cardiovascular and bone remodelling

Université d' Amiens
(Université de Picardie - Jules Verne)
Said Kamel
Amiens

Direct collaboration between bone and vascular experts in same research group.

Research Brief :

Cardiovascular calcifications (CVC) are frequently encountered in the general population. They are associated with a high cardiovascular risk. They are observed with a much greater prevalence in patients with chronic kidney disease (CKD), with diabetes and also in patients with inflammatory diseases such as rheumatoid arthritis. The work done during last few years have allowed us to go along several important research pathways. We are pursuing our work following several of these research lines, in particular the role of the calcium-sensing receptor and that of the uremic toxins, the hemodynamic consequences of CVC, and the identification of novel markers able to predict these soft-tissue calcifications. We are currently evaluating the role of pro-inflammatory mediators in the pathogenesis of CVC, by using experimental models and performing clinical investigations. Our research will focus on the development of innovating therapeutic strategies.
The consequences of our research efforts, based on cell culture models, animal models and human investigation, should be a better understanding of the molecular mechanisms which are responsible for CVC. In addition, our research work should permit an easier detection and more adequate follow-up of the calcification as well as the identification of novel therapeutic targets, with the final goal to improve the care of patients with CVC, in the presence or absence of CKD, who carry a major cardiovascular risk.

- **Methodologies Used :**

Cell culture, cell migration assays (Boyden?s Chamber), molecular biology including MicroRNA
In vitro mineralization assays, osteoclast differentiation
Cranial window technique, isolated cerebral micro-vessel preparation
Echocardiography, pulse wave velocity, cardiac hemodynamics
Ex vivo vascular exploration, histomorphometry

Publications

Maizel J, Six I, Slama M, Tribouilloy C, Sevestre H, Poirot S, Giummelly P, Atkinson J, Choukroun G, Andrejak M, Kamel S, Mazière JC, Massy ZA (2009). Mechanisms of aortic and cardiac dysfunction in uremic mice with aortic calcification., Circulation. 119(2), 306-13

Maizel J, Six I, Dupont S, Secq E, Dehedin B, Barreto FC, Benchitrit J, Poirot S, Slama M, Tribouilloy C, Choukroun G, Mazière JC, Drueke TB, Massy ZA (2013). Effects of sevelamer treatment on cardiovascular abnormalities in mice with chronic renal failure., Kidney Int. 84(3), 491-500.

Hénaut L, Boudot C, Massy ZA, Lopez-Fernandez I, Dupont S, Mary A, Drüeke TB, Kamel S, Brazier M, Mentaverri R (2014). Calcimimetics increase CaSR expression and reduce mineralization in vascular smooth muscle cells: mechanisms of action., Cardiovascular research. 101(2), 256-65

Mary A, Hénaut L, Boudot C, Six I, Brazier M, Massy ZA, Drüeke TB, Kamel S, Mentaverri R. (2015). Calcitriol prevents in vitro vascular smooth muscle cell mineralization by regulating calcium-sensing receptor expression., Endocrinology. 156(6), 1965-74

Tribouilloy C, Rusinaru D, Maréchaux S, Castel AL, Debry N, Maizel J, Mentaverri R, Kamel S, Slama M, Lévy F (2015). Low-gradient, low-flow severe aortic stenosis with preserved left ventricular ejection fraction: characteristics, outcome, and implications for surgery., J Am Coll Cardiol. 65(1), 55-66

Stinghen AE, Massy ZA, Vlassara H, Striker GE, Boullier A (2016). Uremic Toxicity of Advanced Glycation End Products in CKD., J Am Soc Nephrol. 27(2), 354-70

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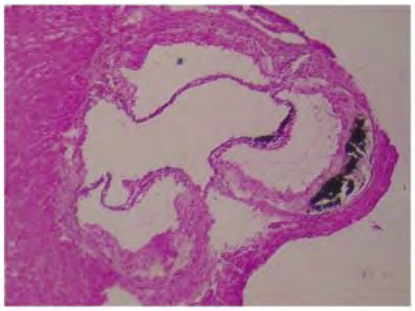
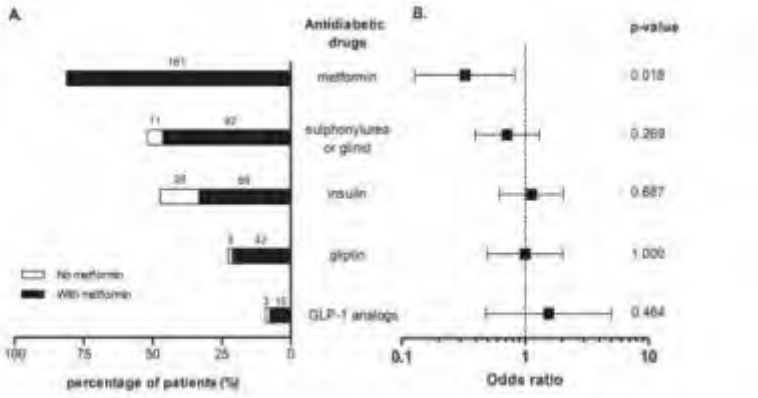
Calcified aortic valve



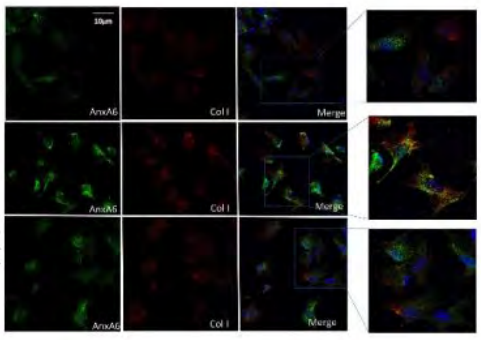
Calcified aortic valve stained with von Kossa in a model of chronic kidney disease Apo E-/- mice .

Association between metformin and vascular calcification in type 2 diabetic patients



Association of antidiabetic drugs with below-knee arterial calcification. A. The histogram represents the frequency of each antidiabetic drug. The black bars indicate patients treated by metformin alone or in combination with other antidiabetic drugs. The white bars indicate patients treated by other antidiabetic drugs without metformin. B. Univariate logistic regression with specific focus on pharmacological antidiabetic therapy

Calcifying matrix vesicles produced by vascular smooth muscle cells.



Interaction between matrix vesicles produced by vascular sooth muscle cells and type I collagen.
Immunofluorescence was assayed using Alexa555-labeled type I collagen (Col I) and Alexa488-labeled Annexin A6 (AnxA6) antibodies. Non permeabilized MOVAS-1 cells were cultured in the absence (Ctrl) or presence of 4 mM phosphate (Pi) for 8 days without or with an inhibitor of vascular calcification. scale: 10 ?m. Boxes highlight the inset region (x3)

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Key facts

Team

- Researchers : 4
- Technicians : 4
- Postdoc fellows : 1
- PhD Students : 4

Translational approaches

- Patents : 3
- Clinical research grants : 5
- Industry partnerships : 1

Keywords

- Heme
- Endothelial activation
- Exosomes
- Microvesicle
- microRNA
- Tunable resistive pulse sensing
- myograph
- flow cytometry

Chantal Boulanger

Endothelial Physiopathology and Biomarkers of Vascular Diseases

Université de Paris 05
(Université Rene Descartes)
Inserm UMR 970
Alain Tedgui
Paris

Associating molecular and integrated physiology to decipher new avenues in the field of endothelial dysfunction

Research Brief :

Cardiovascular diseases are an increasing social and economical burden. An initial step is the loss of vasculo-protective functions of the endothelium. Thus, we need to decipher the mechanisms regulating endothelial dysfunctions to identify new therapeutic targets in vascular diseases. In addition, early detection of dysfunctional endothelial cells will help stratify cardiovascular risk and pharmacological treatment of asymptomatic subjects.
In the past decade we have pioneered research on the release of membrane vesicles (microparticles or microvesicles) from dysfunctional endothelial cells. We have demonstrated that circulating endothelial microparticles (EMP) are potentially useful clinical indicators of dysfunctional endothelium and a prognostic marker of cardiovascular mortality. But extracellular release of membrane vesicles is not only a sign of cell injury, these vesicles are also a new mediators affecting the function of target cells. Indeed we have demonstrated that EMP are paracrine signals for vascular repair in ischemic diseases. In addition, microparticles promote pro-inflammatory and pro-angiogenic responses in human atherosclerotic lesions.

Our current research integrates new research avenues in the field of endothelial dysfunction. We investigate:
1/ the role of autophagy in endothelial activation,
2/ role of micro-RNA packaging in endothelial microvesicles and exosomes in atherosclerosis
3/ the endothelial consequences of erythrocyte activation

• Methodologies Used :

Flow cytometry for cell and microvesicle analysis
Tunable resistive pulse sensing
Endothelial cell culture (murine, human)
Fluorescence microscopy
Myograph for studying isolated blood vessel reactivity
Original murine models with specific endothelial deletion

Publications

Camus SM, Gausserès B, Bonnin P, Loufrani L, Grimaud L, Charue D, De Moraes JA, Renard JM, Tedgui A, Boulanger CM, Tharaux PL, Blanc-Brude OP (2012). Erythrocyte microparticles can induce kidney vaso-occlusions in a murine model of sickle cell disease., Blood. 120(25), 5050-8

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Jean-Sébastien Hulot

Cellular, molecular and physiological mechanisms of heart failure

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Inserm UMR970
Alain Tedgui
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Alliance of high-level basic research and translational medicine

Key facts

Team

- Researchers : 4
- Technicians : 2
- Postdoc fellows : 4
- PhD Students : 3

Translational approaches

- Patents : 4
- Clinical research grants : 2
- Industry partnerships : 5

International research links

- United States
- Germany
- Netherlands

Keywords

- Heart Failure
- Adult Stem Cells
- Gene transfer
- Fibrotic remodeling
- Calcium
- Stem cell biology
- Cytometry / FACS
- cardiomyocyte parameters
- Genome Editing
- iPSC

Biological Resources

- Library of patient-specific hiPSC
- in vivo models: cardiac hypertrophy, myocardial infarction
- Advanced stages of heart failure

Research Brief :

Heart Failure (HF) remains a leading cause of mortality and morbidity in Europe. Our general aims are to understand the molecular and cellular mechanisms involved in the transition to heart failure and to identify relevant targets to reverse the adverse remodeling process or alternatively promote myocardial tissue repair.
During the last years, the team has consequently set up animal and cellular models to study ischemic heart failure (the most prevalent form of HFrEF) as well as cardiac hypertrophy, an adaptive cardiac response to stress (particularly hemodynamic overload) that progressively leads to heart failure (and mimics some stages of HFpEF). In these murine models of heart failure, we have notably identify a new population of adult stem cells that reside in the myocardium and are identified by the expression of PW1/Peg3 gene. We found that these cells are involved in the fibrotic remodelling of the myocardium in response to stress, thus identifying a new target to limit injury-induced adverse remodelling.
More recently the team has developed innovative tools based on human induced pluripotent stem cells to further model cardiac disorders in a dish. This human cellular platform allows to perform pharmacological investigations, model mono- or multigenic forms of cardiomyopathy, investigate underlying pathological pathways and perform direct intervention (genome editing) to correct or introduce punctual genomic changes and perform functional analyses.

• Methodologies Used :

Biology of adult stem cells with appropriate tools to isolate and identify PW1+ cells in all organs including the cardiovascular system
Human cellular models of cardiac disorders using patient-specific hiPSC
Targeted genome editing using TALENS and/or CRISPR/Cas9
Gene transfer in the cardiovascular system using AAV and adenovirus;
Calcium signalling and calcium sources in cardiovascular cells;
Experimental mouse models for heart failure

Publications

KARAKIKES I, STILLITANO F, NONNENMACHER M, TZIMAS C, SANOUDOU D, TERMGLINCHAN V, KONG C-W, RUSHING S, HANSEN J, CEHOLSKI D, KOLOKATHIS F, KREMASTINOS D, KATOULIS A, REN L, COHEN N, GHO J, TSIAPRAS D, VINK A, WU JC, ASSELBERGS FW, LI RA, HULOT JS, KRANIAS E, HAJJAR RJ (2015). Correction of the phospholamban R14Del mutation associated with dilated cardiomyopathy using targeted nucleases and combination therapy, Nature Communications. 6(6955),

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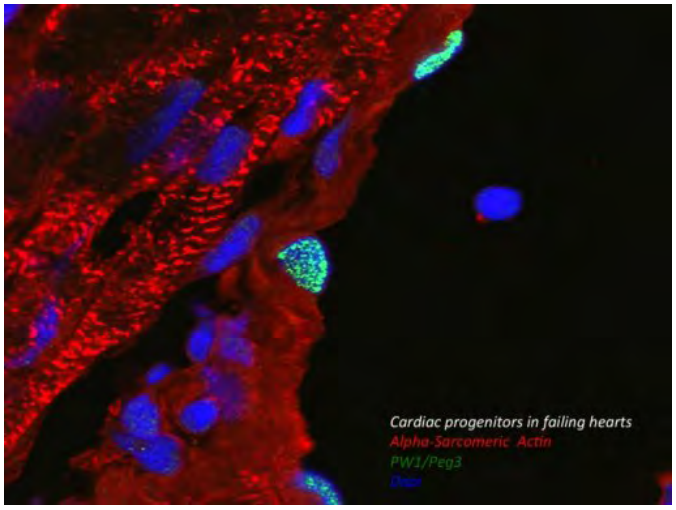
STILLITANO F, HANSEN J, KONG CW, KARAKIKES I, FUNCK-BRENTANO C, GENG L, SCOTT S, REYNIER S, WU M, LAURENT E, VALOGNE Y, PAPADOPOULOS A, DESSEAUX C, SALEM JE, JEZIOROWSKA D, ZAHR N, LI RA, HAJJAR RJ, HULOT JS (2017). Modeling susceptibility to drug-induced long QT with a panel of subject-specific iPS cells, eLife. 6(19406),

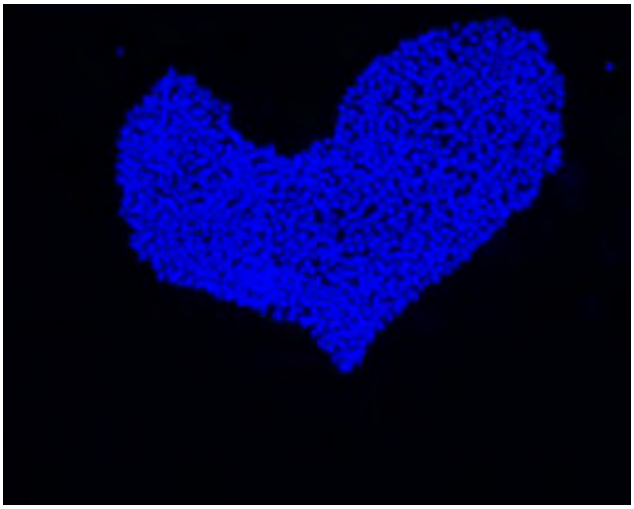
Hulot Jean-Sébastien - jean-sebastien.hulot@aphp.fr - 33156092017

Endogenous Cardiac Stem Cells



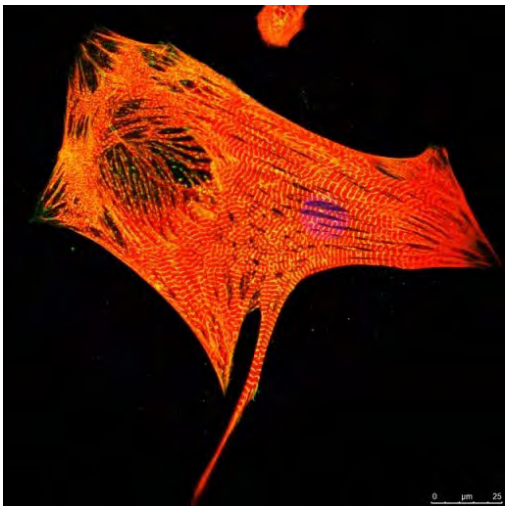
PW1 expression identifies cardiac adult stem cells with fibrogenic potential

Human Models of Cardiac Diseases



A heart-shape colony of human iPS cells

Cardiomyocytes Generated from hiPSC



Human iPS-cell derived cardiomyocytes model cardiac diseases in a dish

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Key facts

Team

• Researchers : 5
• Technicians : 5
• Postdoc fellows : 2
• PhD Students : 2

Translational approaches

• Patents : 0
• Clinical research grants : 6
• Industry partnerships : 1

Keywords

• Rare arterial diseases
• Mitral Valve Prolapse
• Genetics
• Fibromuscular dysplasia
• Gene expression
• Exome sequencing studies
• Genetic association studies
• Knock-out mouse model

Biological Resources

• DNA collection and cohorts of patients with rare inherited vascular disorders
• DNA collection and tissue collection of patients with cardiac valvular diseases (mitral valve prolapse)
• DNA collection and cohort of patients and families with vascular Ehlers Danlos syndrome
• DNA collection and cohort of patients and families with arterial fibromuscular dysplasia

Xavier Jeunemaitre

Genes and rare arterial diseases

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Integrated translational research based on several unique patients cohorts, the constitution and exploitation of DNA and tissue biobanks, the use of the most recent genetic technologies to identify new disease-causing genes and variants, the creation and characterization of cellular and mouse models

Research Brief :

Our team aims to identify causative genes and understand mechanistic basis of several rare arterial diseases. We are interested in rare forms of hypertension (Pseudohypoaldosteronism, type II: PHAII) and Fibromuscular Dysplasia: FMD) and rare vascular diseases : vascular Elhers-Danlos Syndrome (vEDS) and inherited forms of aortic aneurysms (TAA). We have also high interest in understanding the genetics and the biology of mitral valve prolapse (MVP) for which we have recently identified several genetic risk loci.
We apply three complementary strategies to achieve these goals:
1) High throughput genetic and genomic approaches, which are exome sequencing and genome-wide association to families and large cohorts of patients recruited at the Hypertension Department and the National Reference Centre for Rare Vascular Diseases
2) Molecular and physiological investigation in CRISPR-Cas9 engineered cells and animal models of genes involved in the regulation of hypertension and vascular tone: WNK pathway, KLHL3-CUL3 ubiquitin ligase complex and collagen 3 alpha 1 gene COL3A1, mutated in vEDS.
3) Clinical investigation and complications follow-up search of circulating biomarkers and vascular tone assessment for vEDS and FMD patients.

• **Methodologies Used :**

- Human genetic studies : genome-wide association and linkage studies, families and population based cohorts, Exome and targeted sequencing
- Mouse models : transgenesis, gene inactivation, tissue-specific inactivation, in vivo blood pressure monitoring, metabolic cages, arterial myograph, creation of original mouse models
- Tissue characterization : Immunohistochemistry, In situ hybridisation, Confocal microscopy imaging, mRNA quantification, Western blotting, RNA-seq, chromatine interaction
- Cellular models : classical cellular characterization, cell trafficking, inhibition by siRNA and shRNA, original cellular models (SDHB inactivation), ubiquitination process, BRET imaging.

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Publications

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Key facts

Team

- Researchers : 2
- Technicians : 2
- Postdoc fellows : 3
- PhD Students : 3

Translational approaches

- Patents : 3
- Clinical research grants : 0
- Industry partnerships : 0

International research links

- United Kingdom
- Germany
- United States

Keywords

- Protease-activated receptors
- sphingosine-1-phosphate
- kidney disease
- vascular development
- endothelial barrier function
- mouse models of human disease
- autophagy
- mouse genetics and embryology
- cell signaling assays
- intravital microscopy

Biological Resources

- Mouse knockout and transgenic models.
- Bio-banked human kidney biopsies.
- Cohort of sickle cell patients.
- Partnership with the department of Nephrology and Pathology at the Georges Pompidou European Hospital.

Pierre-Louis Tharaux Eric Camerer

GPCRs and Tyrosine Kinase Receptors : Roles and Interactions in Development and Disease

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Using cultured cells, mouse models and human tissue samples, we study the physiological and pathological roles of GPCRs relevant to cardiovascular disease therapy in embryonic development, adult physiology and pathology with focus on kidney, retina, heart and brain.

Research Brief :

Our team aims to unravel fundamental mechanisms that govern the formation and function of blood vessels and the contribution of vascular dysfunction to disease, with a special emphasis on the kidney. The Tharaux group dedicates most of its efforts to identifying and targeting pathological mechanisms that trigger microvascular diseases of the kidney, and is supported by our associate investigators in translational aspects of this research. The Camerer group has several collaborative projects with the Tharaux group, and centers its research on two GPCR families that are critical for vascular development and strives to understand how these receptors are further elicited to contribute to physiological and pathological processes. We ultimately aim to identify pivotal mediators in the control of vascular homeostasis and disease as potential targets for disease prevention. When possible, we take inspiration from clinical studies that inform on the pathways we study and test efficacy and explore unanticipated effects of experimental and approved drugs that target these pathways in the context of our discoveries. Both groups are engaged in a number of national and international collaborations that enrich and complement their research efforts, and have visibility through these partnerships, publications and national and international research conferences.

- **Methodologies Used :**

To address mechanisms of receptor activation, signaling consequences on cellular programming and behavior, and ultimately function, we couple biochemical and cell culture experiments to mouse genetic models of deficiency, gain of function and time- and tissue- specific expression. Our embryonic studies focus on vascular development, while studies in adults focus on microvascular disease.

Publications

Bollée G, Flamant M, Schordan S, Fligny C, Rumpel E, Milon M, Schordan E, Sabaa N, Vandermeersch S, Galaup A, Rodenas A, Casal I, Sunnarborg SW, Salant DJ, Kopp JB, Threadgill DW, Quaggin SE, Dussaule JC, Germain S, Mesnard L, Endlich K, Boucheix C, Belenfant X, Callard P, Endlich N, Tharaux PL. (2011). Epidermal growth factor receptor promotes glomerular injury and renal failure in rapidly progressive crescentic glomerulonephritis., Nature Medicine. 17(1242), 1250

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Gazit SL, Mariko B, Thérond P, Decouture B, Xiong Y, Couty L, Bonnin P, Baudrie V, Le Gall SM, Dizier B, Zoghdani N, Ransinan J, Hamilton JR, Gaussem P, Tharaux PL, Chun J, Coughlin SR, Bachelot-Loza C, Hla T, Ho-Tin-Noé B, Camerer E (2016). Platelet and Erythrocyte Sources of S1P Are Redundant for Vascular Development and Homeostasis, but Both Rendered Essential After Plasma S1P Depletion in Anaphylactic Shock., Circulation Research. 119(e110), E126

Le Gall SM, Szabo R, Lee M, Kirchhofer D, Craik CS, Bugge TH, Camerer E (2016). Matriptase activation connects tissue factor-dependent coagulation initiation to epithelial proteolysis and signaling., Blood. 127(3260), 3269

Henique C, Bollee G, Lenoir O, Dhaun N, Camus M, Chipont A, Flosseau K, Mandet C, Yamamoto M, Karras A, Thervet E, Bruneval P, Nochy D, Mesnard L, Tharaux PL. (2016). Nuclear Factor Erythroid 2-Related Factor 2 Drives Podocyte-Specific Expression of Peroxisome Proliferator-Activated Receptor ? Essential for Resistance to Crescentic GN., J Am Soc Nephrol. 27(172), 188

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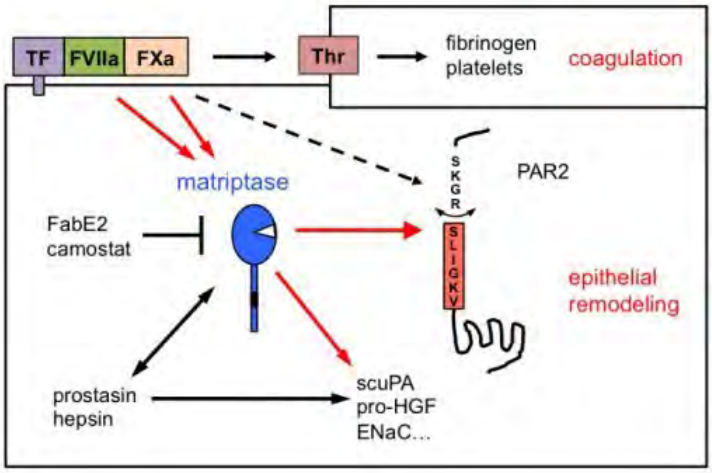
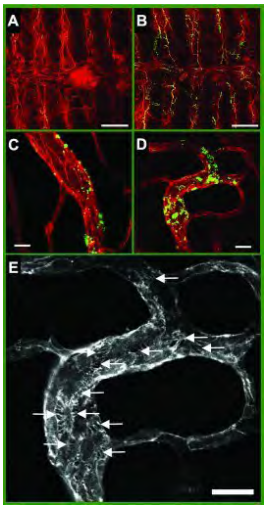
Matriptase connects the coagulation cascade to epithelial signaling and proteolysis.



Schematic representation of how matriptase amplifies coagulation factor signaling in epithelia. Our results suggest that FVIIa and FXa both directly activate matriptase, which in turn activates PAR2 and processes other epithelial substrates. This may connect coagulation activation to epithelial remodeling. Matriptase also mediates PAR2 signaling by the epithelial membrane anchored proteases hepsin and prostasin. Le Gall et al, Blood, 2016

Mice that lack S1P in plasma display enhanced vascular leak.



Control (A,C) and plasma S1Pless (B,D,E) mice were injected i.v. with fluorescent beads and PAF, then perfused with saline 3 minutes later. (A,B) Merged z-stacks at low power with microspheres in green and an endothelial marker in red. (C, D) Representative single plane images at high power. (E) Enlarged image of (D) showing only the red channel. Arrows point to intercellular gaps bridged by filopodia-like extensions. Note increased leak in plasma S1Pless mice. Camerer et al, JCI, 2009

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http://parcc.inserm.fr/research-teams/team/gpcrs-and-tyrosine-kinase-receptors-roles-and-interactions-in-development-and-disease/

Philippe Menasché Jean-Sébastien Silvestre

Regenerative therapies for cardiac and vascular diseases

Paris 5 University
Inserm UMR 970
Alain Tedgui
Paris

The team spans a fully integrated spectrum encompassing basic, preclinical and translational research to develop efficient approaches of cell and non cell-based strategies to circumvent the adverse remodeling occurring in patients with cardiovascular ischemic diseases

Key facts

Team

• Researchers : 3
• Technicians : 3
• Postdoc fellows : 2
• PhD Students : 4

Translational approaches

• Patents : 2
• Clinical research grants : 1
• Industry partnerships : 2

International research links

• USA, Germany, United Kingdom

Keywords

• Extracellular membrane vesicles
• Cardiovascular
• Ischemia
• stem/progenitor cells
• inflammation
• Regeneration
• microangiography
• myocardial infarction
• echocardiography
• Flow Cytometer
• hindlimb ischemia

Biological Resources

• Neonatal model of cardiac regeneration
• In vitro model of cardiac cell differentiation
• Pathophysiological models of postischemic tissue remodeling

Research Brief :

The team is based on the complementary expertise contributed by a group (Dr JS Silvestre) experienced in deciphering of signaling pathways involved in post-ischemic tissue remodeling and a group (Pr P Menasché) with a long?standing experience in the preclinical, translational and clinical aspects of stem cell research. Together, we form an ideal platform of expertise and technical know-how, ranging from the basic features of cell injury, regeneration and remodeling to the clinical applications of cell-based therapies complying with the increasingly stringent regulatory requirements. The background of the group members (both basic scientists and practising clinicians) as well as their respective expertises allow the team to cover a spectrum of activities from the mechanisms of postischemic tissue remodelling and regeneration at the molecular level to the development of therapeutic strategies to mimick and boost these processes. Through the use of tools ranging from molecular biology methods to small and large animal models, the team spans a fully integrated spectrum encompassing basic, preclinical and translational research. Our main objectives are to decipher the molecular and cellular mechanisms involved in post-ischemic tissue remodeling and to develop efficient approaches of cell-based strategies to circumvent the adverse remodeling occurring in patients with cardiovascular diseases.

• **Methodologies Used :**

- Pathophysiological models of postischemic tissue remodeling: hindlimb ischemia induced by right femoral artery ligation and cardiac ischemia induced by occlusion of the proximal left anterior descending coronary artery
- Vessel growth analysis by high definition microangiography, immunohistochemistry and laser Doppler imaging to analyze flow recovery
- Transthoracic echocardiography to follow non-invasively systolic and diastolic ventricular function
- Transthoracic echo-guided injection
- Flow cytometer: FACS sorter, Image stream

Publications

Rueda P, Richart A, Récalde A, Gasse P, Vilar J, Guérin C, Lortat-Jacob H, Vieira P, Baleux F, Chretien F, Arenzana-Seisdedos F, Silvestre JS. (2012). Homeostatic and Tissue Reparation Defaults in Mice Carrying Selective Genetic Invalidation of CXCL12/Proteoglycan Interactions., Circulation. 1260(15), 1882-95

Zouggari Y, Ait-Oufella H, Bonnin P, Simon T, Sage AP, Guérin G, Vilar J, Caligiuri G, Tsiantoulas D, Laurans L, Dumeau E, Kotti K, Bruneval K, Charo IF, Binder CJ, Danchin N, Tedgui A, Tedder TF, Silvestre JS/Mallat Z*. (2013). B lymphocytes trigger Ccl7-dependent mobilization of monocytes and promote adverse ventricular remodeling after acute myocardial infarction, Nat Med. 190(10), 1273-80*

Menasché P, Vanneaux V, Hagège A, Bel A, Cholley B, Cacciapuoti I, Parouchev A, Benhamouda N, Tachdjian G, Tosca L, Trouvin JH, Fabreguettes JR, Bellamy V, Guillemain R, Suberbielle Boissel C, Tartour E, Desnos M, Larghero J (2015). Human embryonic stem cell-derived cardiac progenitors for severe heart failure treatment: first clinical case report., Eur Heart J. 7(36), 2011-7

Kervadec A, Bellamy V, El Harane N, Arakélian L, Vanneaux V, Cacciapuoti I, Nemetella H, Périer MC, Toeg HD, Richart A, Lemitre M, Yin M, Loyer X, Larghero J, Hagège A, Ruel M, Boulanger CM, Silvestre JS, Menasché P, Renault NKE (2016). Cardiovascular Progenitor-Derived Extracellular Vesicles Recapitulate the Beneficial Effects of their Parent Cells in the Treatment of Chronic Heart Failure, J Heart Lung Transplant. 35(6), 795-807

Ngkelo A, Richart A, Kirk JA, Bonnin P, Vilar J, Lemitre M, Marck P, Branchereau M, Le Gall S, Renault N, Guerin C, Ranek MJ, Kervadec A, Danelli L, Gautier G, Blank U, Launay P, Camerer E, Bruneval P, Menasche P, Heymes C, Luche E, Casteilla L, Cousin B, Rodewald HR, Kass DA, Silvestre JS (2016). Mast cells regulate myofilament calcium sensitization and heart function after myocardial infarction, J Exp Med. 27(213), 1353-74

Howangyin KY, Zlatanova I, Pinto C, Ngkelo A, Cochain C, Rouanet M, Vilar J, Lemitre M, Stockmann C, Fleischmann BK, Mallat Z, Silvestre JS (2016). Myeloid-Epithelial-Reproductive Receptor Tyrosine Kinase and Milk Fat Globule Epidermal Growth Factor 8 Co-Ordinately Improve Remodeling After Myocardial Infarction via Local Delivery of Vascular Endothelial Growth Factor, Circulation. 133(9), 826-39

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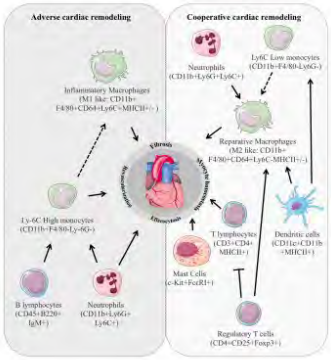
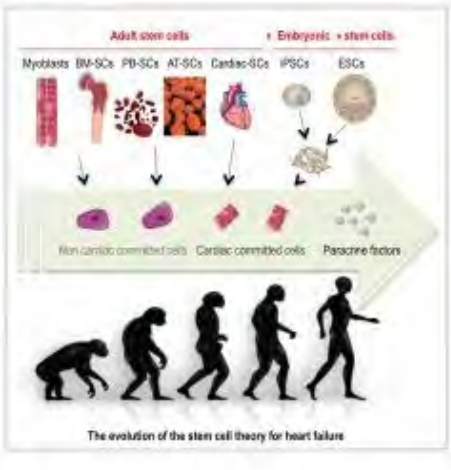
Inflammation and cardiac repair



Immune cell stimulation is among the earliest responses detectable in the injured cardiac tissue and plays an instrumental role in the coordination of multiple processes governing cardiac remodeling. In animal models, the number, type and activation state of the different subclasses of inflammatory cells dictate their impact on cardiac repair leading to either positive or deleterious cardiac remodeling. (From Zlatanova et al, Front Cardiovasc Med, 2016)

The evolution of the stem cell theory for heart failure



The recent big bang in the evolution of the stem cell theory suggests that therapeutic cells rather act as reservoirs of a wide array of bioactive entities that trigger multiple and synergic endogenous repair pathways. Abbreviations: BM: bone marrow, PB: peripheral blood; AT: adipose tissue; iPSCs: induced pluripotent stem cells; ESCs: embryonic stem cells; SCs: stem cells. (From Silvestre JS/P Menasché, Ebiomedicine, 2015)

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Key facts

Team

• Researchers : 1
• Technicians : 1
• Postdoc fellows : 1
• PhD Students : 0

Translational approaches

• Patents : 2
• Clinical research grants : 0
• Industry partnerships : 2

International research links

• USA
• Japan
• Austria, Sweden, Germany

Keywords

• hypoxia
• innate immunity
• tumor microenvironment
• angiogenesis
• fibrosis
• Flow cytometry
• transgenic mouse models
• Histology

Biological Resources

• conditional in vivo deletions in innate immune cell subsets of Hypoxia-inducible factors, von Hippel Lindau Protein, VEGF

Christian Stockmann

INFLAMMATORY VASCULAR REMODELING AND MICROENVIRONMENTAL HOMEOSTASIS

Université Paris Descartes
Paris 5
Inserm U 970
Alain Tedgui
Paris

We define inflammation-driven vascular remodeling as central interconnection between cancer progression, organ fibrosis and physiological tissue regeneration!

Research Brief :

The infiltration of inflammatory cells into hypoxic tissue microenvironments and subsequent formation of new blood vessels (angiogenesis) or remodeling of the existing vasculature are central features of physiological wound healing responses as well as the pathophysiological processes of tumor angiogenesis and tissue fibrosis.

We aim to

(i) decipher how inflammatory cell-driven remodeling of the vasculature affects these processes

(ii) develop therapeutic strategies to target deleterious effects as well as to exploit the beneficial impact of the inflammatory response and vascular remodeling.

• **Methodologies Used :**

transgenic mouse models
in vivo models of cancer, organ fibrosis and tissue regeneration
in vivo, real time imaging of angiogenesis and tissue hypoxia
Flow cytometry
immunohistochemistry

Publications

Stockmann C, Kerdiles Y, Nomaksteinsky M, Weidemann A, Takeda N, Doedens A, Torres-Collado AX, Iruela-Arispe L, Nizet V, Johnson RS (2010). Loss of myeloid cell-derived vascular endothelial growth factor accelerates fibrosis, Proc Natl Acad Sci U S A. 107(), 4329-34

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Kantari-Mimoun S, Castells M, Klose R, Meinecke AK, Lemberger UJ, Rautou PE, Pinot-Roussel H, Badoual C, Schrödter K, Osterreicher CH, Fandrey J, Stockmann C (2015). Resolution of liver fibrosis requires myeloid cell-driven sinusoidal angiogenesis, Hepatology. 61(6), 2042-55

Ralph Klose, Ewelina Krzywinska, Magali Castells, Dagmar Gotthardt, Eva Maria Putz, Chahrazade Kantari-Mimoun, Naima Chikdene, Anna-Katharina Meinecke, Katrin Schrödter, Iris Helfrich, Joachim Fandrey, Veronika Sexl & Christian Stockmann (2016). Targeting VEGF-A in myeloid cells enhances natural killer cell responses to chemotherapy and ameliorates cachexia, Nat Commun. 19(7), 12528

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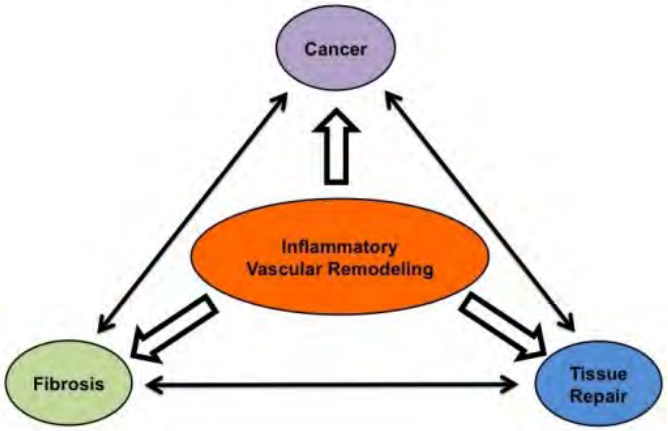
http://parcc.inserm.fr/research-teams/team/inflammatory-vascular-remodeling-and-microenvironmental-homeostasis/



Inflammation-driven vascular remodeling as central connection between cancer, tissue regeneration and fibrosis

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Key facts

Team

• Researchers : 6
• Technicians : 3
• Postdoc fellows : 2
• PhD Students : 3

Translational approaches

• Patents : 4
• Clinical research grants : 2
• Industry partnerships : 2

International research links

• Canada, USA, Spain, Switzerland

Keywords

• Brain
• Angiotensins
• Apelin
• Monozinc aminopeptidases
• G-protein coupled receptors
• Vasopressin/water balance
• Blood pressure
• Cardiac function
• drinking behavior
• enzymatic activity
• neuropeptide radioimmunoassay
• Western-blot
• expression of proteins
• Confocal microscopy
• in situ hybridization
• immunohistochemistry
• internalization
• [Ca2+]i mobilization
• signaling
• binding
• cellular biology
• molecular biology
• diuresis
• vessel vasoreactivity
• blood pressure
• cardiac function
• hypertension
• myocardial infarction
• heart failure
• Molecular modelling

Biological Resources

• experimental model of heart failure after myocardial infarction (mouse)
• experimental model of hypertension (rat)
• experimental model of hyponatremia

Catherine Llorens-Cortes

Neuropeptides Centraux et Régulations Hydrique et Cardiovasculaire -Central neuropeptides in the regulation of body fluid homeostasis and cardiovascular functions

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Alain Prochiantz
Paris

Our work is to identify new therapeutic targets (enzymes involved in the metabolism of (neuro)vasoactive peptides or their receptors) involved in water balance and cardiovascular functions control. The synthesis of compounds acting on these targets leads to the development of therapeutic agents.

Research Brief :

BRAIN RENIN-ANGIOTENSIN SYSTEM (RAS). We showed in the brain RAS that aminopeptidase A (APA) generates angiotensin III (AngIII) from AngII and that brain AngIII exerts a tonic stimulatory effect on the control of blood pressure (BP) in hypertensive animals. In coll. with the team of B. Roques (U640), we designed the first specific and selective APA inhibitor, EC33 and we showed that the inhibition of brain APA decreases BP. Brain APA constitutes a potential therapeutic target for the treatment of hypertension. We produced a new APA inhibitor, RB150 able, after administration by oral route, to cross the intestinal, hepatic and blood brain barriers, to block the activity of the brain RAS and to normalize BP in hypertensive animals. We pursue the preclinal development of RB150 with Quantum Genomics. APELINERGIC SYSTEM. We isolated an orphan receptor which was shown to be the receptor of a new peptide, apelin. We demonstrated that apelin and its receptor are expressed together with vasopressin (AVP) in hypothalamic neurons. We showed that the icv injection of apelin in lactating rats decreased the activity of these neurons and the systemic secretion of AVP, resulting in aqueous diuresis. Apelin is a natural inhibitor of the anti-diuretic effects of AVP. We showed that in rats and humans, apelin and AVP are regulated in opposite manners by osmotic stimuli. In addition, apelin decreases BP, improves cardiac contractility. Apelin controls water balance and cardiovascular functions.

• **Methodologies Used :**

Molecular modeling and molecular biology: 3D model of enzyme or GPCRs and site-directed mutagenesis studies - Screening of chemical libraries - Pharmacological studies of GPCRs stably expressed in eukaryotic cells : binding, cAMP production, [Ca2+]i mobilization, internalization followed by confocal microscopy - Neuroanatomical studies: immunohistochemistry, in situ hybridization - Purification of peptides by HPLC and radioimmunoassay - Enzymatic studies: expression of recombinant enzymes, purification, Western-blot analysis, enzymatic activity - Physiological studies: measurement of vasopressin release, drinking behavior, diuresis, plasma and urinary electrolytes Vessel vasoreactivity - Blood pressure - Cardiac function

Publications

Marc Y, Gao J, Balavoine F, Michaud A, Roques BP, Llorens-Cortes C (2012). Central antihypertensive effects of orally active aminopeptidase A inhibitors in spontaneously hypertensive rats., Hypertension. 60(2), 411-8

Huang B.S, Ahmad M, White R.A, Marc Y, Llorens-Cortes C, Leenen F.H.H. (2013). Inhibition of brain angiotensin III by aminopeptidase A inhibitor attenuates sympathetic hyperactivityand cardiac dysfunction in rats post myocardial infarction, CARDIOVASC. RES.. 97(3), 424,-31

Balavoine F, Azizi M, Bergerot D, De Mota N, Patouret R, Roques B.P, Llorens-Cortes C. (2014). Randomised, Double-Blind, Placebo-Controlled, Dose-Escalating Phase I Study of QGC001, a Centrally Acting Aminopeptidase A Inhibitor Prodrug., CLIN. PHARMACOKINET.. 53(4), 385-95

Gerbier R, Leroux V, Couvineau P, Alvear-Perez R., Maigret B, Llorens-Cortes C, Iturrioz X*. *Co-Last Authors (2015). New structural insights into the apelin receptor: identification of key residues for apelin binding., The FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 29(1), 314-22*

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Key facts

Team

• Researchers : 3
• Technicians : 2
• Postdoc fellows : 2
• PhD Students : 3

Translational approaches

• Patents : 2
• Clinical research grants : 2
• Industry partnerships : 0

Keywords

• hypoxia
• angiogenesis
• ischemic cardiovascular diseases
• vascular biology
• cancer
• microscopy
• biomarkers
• animal models
• cell culture
• Translational Studies

Biological Resources

• Biobank (DNA, serum and plasma): Tumor bank (Hopital Saint-Louis); Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS)
• Human vascular tissues and cell biobank
• Animal models of angiogenesis and lymphangiogenesis (tumor models, metastatic models, ischemic models, lymphangioma)
• Primary culture (Venous and arterial endothelial and vascular smooth muscle cells)
• Ex vivo models of angiogenesis and lymphangiogenesis (arterial rings, lymphatic thoratic duct assay)
• Experimental models of acute myocardial infarction and stroke (mouse, rat and rabbit)

Stéphane Germain

Role of Matrix Proteins in Hypoxia and Angiogenesis

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Inserm U1050 CNRS
Alain Prochiantz
Paris

Our goal is to understand how endothelial cells respond to hypoxia in order to identify new specific markers of hypoxia-induced angiogenesis and new potential therapeutic targets in cancer and ischemic cardiovascular diseases

Research Brief :

Biological events that permits an organism to maintain tissue viability in hypoxia remains poorly understood. How hypoxic endothelial cells integrate chemical signals with mechanical cues from their local microenvironment to protect vascular integrity during ischemic insult and/or induce functional capillary networks that exhibit specialized form remains an open question. A key role of hypoxia in regulating endothelial function is nevertheless established and growing evidence shows that angiogenesis, blood vessels formation by sprouting or growth of preexisting vessels, can be triggered by hypoxia, both during development and in pathological conditions.
Our efforts have recently been focused on characterizing the role of Lysyl Oxidase-like 2, Thrombospondin-1 and Angiopoietin-like 4 in regulating angiogenesis and vascular integrity. The complementary technical expertise of the members of the team together with the established collaborations with clinicians (Pathology, Urology, Cancer and Biochemistry departments, Hopital Saint-Louis and HEGP) led to the definition of angptl4 mRNA as an accurate marker for primary ccRCC diagnosis. Altogether, our studies aimed at better understanding of the complex interplay between endothelial cells and soluble growth factors and mechanical factors from the extracellular matrix will certainly have significant implications for understanding the regulation of developmental and pathological angiogenesis driven by hypoxia.

• **Methodologies Used :**

Multidisciplinary approach combining gene discovery approach for complex human diseases
- Cell culture, cell biology: vascular cell proliferation, adhesion, migration, cell velocity, videomicroscopy, 2-D and 3-D angiogenesis models, normoxia, hypoxia
- Gene/protein structure function analysis (molecular biology, transcriptomics, extracellular matrix proteomics, transfection, mutagenesis)
- Animal models, transgenic mice, cardiovascular functional exploration, cancer, metastases
- Vascular development (animal models, zebrafish studied by confocal, second harmony, bi-photon, and electron microscopy)

Publications

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The interaction of HSPGs with endothelial transglutaminase-2 limits VEGF165--induced angiogenesis

Online Cover This week features a Research Article that shows that transglutaminase-2 prevents heparan sulfate from potentiating signaling by a specific VEGF isoform, thereby attenuating blood vessel formation. The image shows retinal vascularization in a mouse deficient in transglutaminase-2

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Antonino Nicoletti

Immunopathology and immunomodulation of cardiovascular diseases

Université de Paris 07
(Université Denis Diderot)
Inserm U1148
Didier Letourneur
Paris

Double expertise in Vascular Biology and Immunology

Key facts

Team

- Researchers : 3
- Technicians : 4
- Postdoc fellows : 1
- PhD Students : 4

Translational approaches

- Patents : 3
- Clinical research grants : 0
- Industry partnerships : 1

Keywords

- Atherosclerosis
- Immunology
- Flow cytometry
- Microscopy

Biological Resources

- Various strains of mice: CD31 KO, CD31 Tg, ApoE KO, actin GFP Tg, OT2 TCR Tg, LTßR KO, Qa-1KO

Research Brief :

It is nowadays recognized that a crucial immune pathogenetic component contributes to atherogenesis. Our team works on the immune mechanisms and on the signaling pathways involved in atherogenesis. Our projects encompass molecular aspects as well as integrative pathophysiology and aim at discovering new pronostic, diagnostic, and therapeutic tools.
Two main research programs are currently developed:
1) The adventitial lymphoid neogenesis concentrates the main actors of the adaptive immunity. We wish to characterize these lymphoid structures and understand their pathogenic role.
2) The CD31 is an inhibitor of inflammation and we have discovered that is can be shed on activated lymphocytes. We are setting up molecular strategies able to restore the CD31 signaling.

- **Methodologies Used :**

Polychromatic flow cytometry
6D microscopy
Experimental models
Cell immunobiology

Publications

Fornasa, G., Groyer, E., Clement, M., Dimitrov, J., Compain, C., Gaston, A. T., Varthaman, A., Khallou-Laschet, J., Newman, D. K., Graff-Dubois, S., Nicoletti, A. and Caligiuri, G. (2010). TCR stimulation drives cleavage and shedding of the ITIM receptor CD31, J Immunol. 184(10), 5485-92

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Key facts

Team

- Researchers : 8
- Technicians : 3
- Postdoc fellows : 1
- PhD Students : 4

Translational approaches

- Patents : 0
- Clinical research grants : 5
- Industry partnerships : 7

Keywords

- translational research
- heart failure
- Biomarkers
- diabetes
- exercise
- Biobanks
- animal models

Biological Resources

- In vivo animal models of heart failure
- Cohorts
- Biobanks

Alain Cohen Solal

Biomarkers and Heart Failure

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Alain Cohen Solal
Paris

Our team is unique as it has mounted a large local, national et international networks on biomarkers in heart diseases, mainly heart failure. It performs translational research in small animal models of heart failure where the new biomarkers are tested (tissue location and functional significance)

Research Brief :

Our team, composed of clinical and basic science searchers, works at discovering and validation new biomarkers in cardiac diseases, mainly heart failure. We use biobank data in our lab with samples coming from national and international collaborators connected in a network (GREAT). We also performed translational research as our biomarkers as tested in small heart failure animal models, especially in terms of tissue location and functionality.

- **Methodologies Used :**

Biobank
International multicenter registries and trials
Translational research (small animal models of models of heart failure)
Echocardiography, exercise testing
Immunohistochemistry, PCR, western blots, Elisa, tissue engineering

Publications

Papaioannou V1, Mebazaa A, Plaud B, Legrand M. (2014). Chronomics' in ICU: circadian aspects of immune response and therapeutic perspectives in the critically ill., Intensive Care Med Exp.. 2(1), 18

Vodovar N, Séronde MF, Laribi S, Gayat E, Lassus J, Boukef R, Nouira S, Manivet P, Samuel JL, Logeart D, Ishihara S, Cohen Solal A, Januzzi JL Jr, Richards AM, Launay JM, Mebazaa A; GREAT Network.. (2014). Post-translational modifications enhance NT-proBNP and BNP production in acute decompensated heart failure., Eur Heart J.. 35(48), 3434-3441

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Arrigo M, Truong QA, Onat D, Szymonifka J, Gayat E, Tolppanen H, Sadoune M, Demmer RT, Wong KY, Launay JM, Samuel JL, Cohen-Solal A, Januzzi JL Jr, Singh JP, Colombo PC, Mebazaa A. (2017). LSoluble CD146 Is a Novel Marker of Systemic Congestion in Heart Failure Patients: An Experimental Mechanistic and Transcardiac Clinical Study., Clin Chem. 63(), 386-393

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Key facts

Team

- Researchers : 8
- Technicians : 1
- Postdoc fellows : 0
- PhD Students : 5

Translational approaches

- Patents : 1
- Clinical research grants : 1
- Industry partnerships : 1

Keywords

- heart
- excitation-contraction coupling
- RyR
- Ca2+ sparks
- Ca2+ channel
- Epac
- small G proteins
- aldosterone
- arrhythmia
- heart failure
- cardiac hypertrophy
- patch-clamp
- molecular biology
- confocal microscopy
- biochemistry
- bilayers

Biological Resources

- adult rodent cardiac myocytes
- neonatal cardiac myocytes
- adenovirus
- mouse sinus node preparation
- transgenic mice breeding

Ana Maria Gomez

Calcium Signaling and Cardiovascular Physiopathology

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(Université Paris Sud)
Inserm UMR-S 1180
Ana Maria Gomez
Chatenay Malabry

Our team has the internationally recognized expertise in cardiac excitation-contraction coupling in physiologic and pathologic conditions and in molecular basis of arrhythmia. We are one of the rare teams that combine simultaneous recordings of patch-clamp and confocal microscopy in cardiomyocytes.

Research Brief :

Cardiovascular diseases remain the leading cause of death in developed countries. Last stage of cardiac pathologies, heart failure (HF) is major cause of morbidity and mortality. HF patient?s prognostic is very poor, and about 50% die suddenly as consequence of arrhythmia. This is the consequence of misunderstanding of the mechanisms responsible of contractile dysfunction and arrhythmogenesis. In addition of activating cardiac contraction, Ca2+ is recently emerging as a key factor in transcription regulation (excitation-transcription coupling) and in arrhythmia development.
Our project aims to elucidate the adaptive and maladaptive mechanisms involved in HF and arrhythmia, focusing on compartmentalized intracellular Ca2+ signals, through the Ca2+ release channel, the ryanodine receptor (RyR) and the molecular pathways involved in its malfunction. We will focus on a cAMP-directly activated protein named Epac and in the hormone aldosterone, whose expressions are increased in HF, but also in the cardiotoxic effects of anticancer therapies. We have shown a major role of Epac and aldosterone in Ca2+ handling. We will analyze their role in HF and arrhythmia. Moreover, mutations in the RyR are responsible of lethal arrhythmia. We have shown functional consequences of a mutation in the C terminal portion of the RyR. Our project is to analyze a new mutation in the N-terminal portion of the channel.

- **Methodologies Used :**

- Electrophysiology : patch-clamp and lipid bilayers
- Confocal Microscopy (alone or coupled to patch-clamp)
- Superresolution Gated STED
- Biochemistry, molecular and cellular biology.
- Transgenic animal breeding
- Holter telemetry

Publications

Neco P, Torrente AG, Mesirca P, Zorio E, Liu N, Priori SG, Napolitano C, Richard S, Benitah JP, Mangoni ME, Gómez AM. (2012). Paradoxical effect of increased diastolic Ca(2+) release and decreased sinoatrial node activity in a mouse model of catecholaminergic polymorphic ventricular tachycardia., Circulation. 126(4), 392-401

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Sabourin J, Bartoli F, Antigny F, Gomez AM, Benitah JP. (2016). Transient Receptor Potential Canonical (TRPC)/Orai1-dependent Store-operated Ca2+ Channels: NEW TARGETS OF ALDOSTERONE IN CARDIOMYOCYTES., J Biol Chem. 291(25), 13394-409

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Grégoire Vandecasteele

Cyclic Nucleotide Signaling and Cardiovascular Pathophysiology

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Inserm UMR-S1180
Ana-Maria Gomez
Châtenay-Malabry

Our team demonstrated that cAMP signalling in heart and vessels is highly compartmentalized through the activity of specific cAMP-PDEs and that a loss in cAMP compartmentation occurs during cardiac pathological hypertrophy and contributes to the development of heart failure.

Key facts

Team

- Researchers : 8
- Technicians : 4
- Postdoc fellows : 2
- PhD Students : 6

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 1

International research links

- Germany
- United States
- Italy

Keywords

- cAMP-dependent protein kinase
- phosphodiesterase
- ion channels
- heart failure
- compartmentation
- electrophysiology
- excitation-contraction coupling
- FRET-based imaging
- echocardiography
- vascular reactivity

Biological Resources

- Rat/mouse models of heart failure (TAC, MI)

Research Brief :

Heart failure (HF) is the only cardiovascular disease that is increasing in prevalence in Europe and the USA. Most cases of HF are caused by diseases of heart muscle that result in pathologic hypertrophy ("remodeling" at the ventricular chamber level) and contractile dysfunction. The majority of HF in patients under 70 years of age reflects impaired systolic function resulting from dilated cardiomyopathy. Beta-adrenergic receptor/cAMP cascade is centrally involved in the pathophysiology of HF, as demonstrated by the correlation between elevated norepinephrine and mortality and the beneficial effect of beta-blockers in this pathology. However, such medications are effective in only 40-50% of HF patients. In the recent past, our team has crucially contributed to the understanding that physiological cAMP signaling is confined in specific subcellular domains and suggested that drawbacks of HF treatments are due to their bypass of compartmentalization. The goal of our team is to provide an in-depth analysis of cAMP signaling in pathologic hypertrophy and to define defective cAMP signaling events that underlie HF. Since HF is associated with anomalies of the vasomotor tone, we also explore the organization of the cAMP signaling cascade in vascular smooth muscle.

- **Methodologies Used :**

Our studies are conducted in rat, mouse and humans. Experimental approaches combine assessment of cardiac function in vivo (echocardiography, ECG) and at the organ level (Langendorff perfused heart), and single cell (patch-clamp, fluorescence imaging) and biochemical studies. A major focus is placed on cAMP phosphodiesterases (PDE) and protein kinase A because our previous work has demonstrated that these enzymes play a key role in the organization of the intracellular cAMP cascade. Through the development of molecules that activate specific cardiac PDE isoforms, our project will attempt to provide new treatments of HF acting on localized cAMP signaling to improve heart function and clinical outcomes.

Publications

Molina CE, Leroy J, Richter W, Xie M, Scheitrum C, Lee IO, Maack C, Rucker-Martin C, Donzeau-Gouge P, Verde I, Llach A, Hove-Madsen L, Conti M, Vandecasteele G and Fischmeister R. (2012). Cyclic adenosine monophosphate phosphodiesterase type 4 protects against atrial arrhythmias., Journal of the American College of Cardiology. 59(), 2182-2190

Haj Slimane Z, Bedioune I, Lechene P, Varin A, Lefebvre F, Mateo P, Domergue-Dupont V, Dewenter M, Richter W, Conti M, El-Armouche A, Zhang J, Fischmeister R, Vandecasteele G. (2014). Control of cytoplasmic and nuclear protein kinase a by phosphodiesterases and phosphatases in cardiac myocytes, Cardiovascular Research. 102(), 97-106

Hubert F, Belacel-ouari M, Manoury B, Zhai K, Domergue-dupont V, Mateo P, Joubert F, Fischmeister R and Leblais V. (2014). Alteration of vascular reactivity in heart failure: role of phosphodiesterases 3 and 4., British Journal of Pharmacology. 171(), 5361-5375

Bobin P, Varin A, Lefebvre F, Fischmeister R, Vandecasteele G and Leroy J. (2016). Calmodulin kinase II inhibition limits the pro-arrhythmic Ca2+ waves induced by cAMP-phosphodiesterase inhibitors., Cardiovascular Research. 110(), 151-161

Vettel C, Lindner M, Dewenter M, Lorenz K, Schanbacher C, Riedel M, Lammle S, Meinecke S, Mason FE, Sossalla S, Geerts A, Hoffmann M, Wunder F, Brunner FJ, Wieland T, Mehel H, Karam S, Lechene P, Leroy J, Vandecasteele G, Wagner M, Fischmeister R, El-Armouche A. (2017). Phosphodiesterase 2 protects against catecholamine-induced arrhythmia and preserves contractile function after myocardial infarction., Circulation Research. 120(), 120-132

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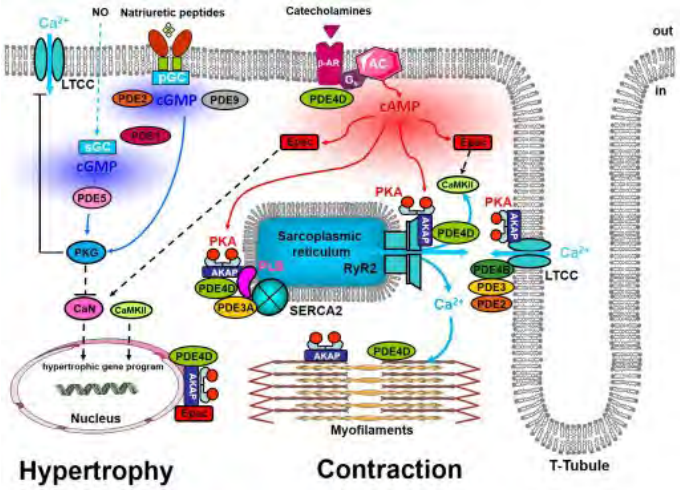
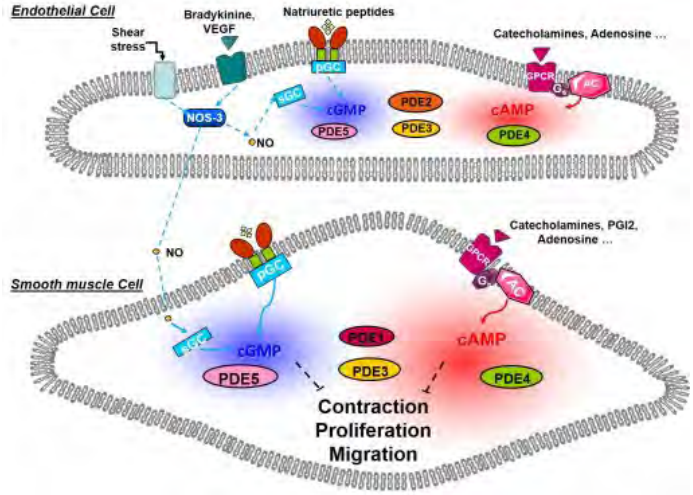
Cyclic nucleotides metabolism in cardiac myocytes.



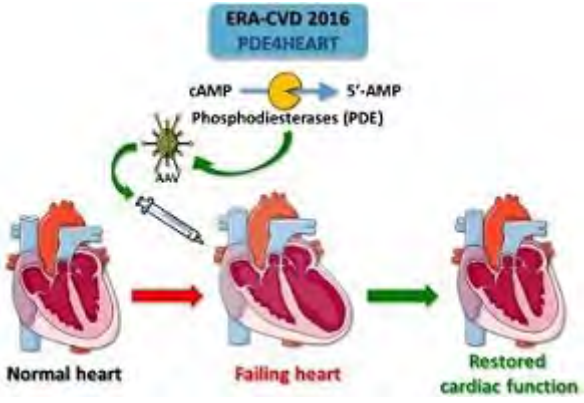
The major phosphodiesterases (PDEs) expressed in cardiac myocytes are indicated, together with their subcellular localization in relation to their role in regulating hypertrophic growth and excitation-contraction coupling. AC: adenylate cyclase; AKAP: A-kinase anchoring protein; CaMKII: Ca2+/calmodulin-dependent kinase II; cAMP: cyclic adenosine monophosphate. Adapted from Bobin et al. Arch Cardiovasc Dis. 2016.

Cyclic nucleotide metabolism in vascular endothelial and smooth muscle cells.



Cyclic nucleotide metabolism in vascular endothelial and smooth muscle cells. For each cell type, the main pathways leading to cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) synthesis and the major phosphodiesterase (PDE) families involved in their degradation are indicated. GPCR: G-protein coupled receptor; Gs: heterotrimeric G-protein stimulating AC; NO: nitric oxide; NOS: NO synthase; pGC: particulate guanylate cyclase.

Gene therapy with phosphodiesterases to treat heart failure



The figure illustrates one of the current research project of the team supported by the European Research Area Network (ERA-Net) on Cardiovascular diseases and involving three other european teams (FO Levy, Norway; V Nikolaev, Germany; E Hirsch, Italy). Our goal is to test whether augmenting the activity of a cAMP phosphodiesterase (PDE) in the heart by gene therapy with adeno-associated virus (AAV) is beneficial in heart failure.

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Key facts

Team

- Researchers : 5
- Technicians : 1
- Postdoc fellows : 2
- PhD Students : 2

Translational approaches

- Patents : 2
- Clinical research grants : 1
- Industry partnerships : 1

International research links

- Germany, Austria, Italy, England, USA, Thailand

Keywords

- cardiac arrhythmias
- apoptosis
- ischemia-reperfusion injury
- electrophysiology
- pacemaker activity
- Patch clamp recording
- Confocal imaging of intracellular Ca2+ handling
- Genetically-modified mouse models of dysfunction in cardiac pacemaking
- Cardiac exploration ex vivo (isolated heart) and in vivo (echography; telemetry)
- Mouse models of ischemia-reperfusion injury

Biological Resources

- in vivo and in vitro models of heart disease
- surgical models
- genetic models

Stéphanie Barrère - Lemaire Matteo Mangoni

Cardiac Physiopathology and Cardioprotection

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We developed worldwide unique mouse models to investigate the mechanisms underlying dysfunction of heart automaticity. We dissect the signaling mechanisms involving the death-receptor apoptotic pathway in ischemia-reperfusion injury.

Research Brief :

Our research aims to develop strategies to protect the heart from dysfunction of impulse generation and ischemic injury. We aim to understand the mechanisms underlying the genesis and regulation of heart rate, an important determinant of morbidity and mortality. We were the first to develop in vitro electrophysiological studies on mouse sino-atrial (SAN) and atrioventricular (AVN) cells associated to confocal live imaging of calcium. Our strategy is based on the use of genetically modified mouse models to identify the contribution of the ion channels and intracellular calcium release in the generation and regulation of cardiac automaticity associated with in vivo experiments using telemetry on freely moving mice. We also aim to understanding the mechanisms underlying cell death and the cardioprotective effect of postconditioning protocols to prevent reperfusion injuries after infarction. We have evidenced the importance of the Fas-dependent pathway and the major role of the adaptator protein DAXX. The inactivation of the extrinsic pathway is associated to a large reduction in infarct size . Our therapeutical strategies are based on inhibiting reperfusion-induced apoptosis. We aim now at dissecting the mechanisms of Postconditioning protocols and the molecular determinants of the apoptotic cascade related to death receptors activation. Translational clinical studies on cardioprotection are also developed.

- **Methodologies Used :**

Patch clamp recording
Confocal imaging of intracellular Ca2+ dynamics
Cardiac exploration ex vivo (isolated heart) and in vivo (echography, telemetry)
Genetically-modified mouse models of cardiac automaticity and impulse conduction
Mouse models of ischemia-reperfusion injury

Publications

Roubille F, Franck-Miclo A, Covinhes A, Lafont C, Cransac F, Combes S, Vincent A, Fontanaud P, Sportouch-Dukhan C, Redt-Clouet C, Nargeot J, Piot C, Barrère-Lemaire S (2011). Delayed postconditioning in the mouse heart in vivo., Circulation. 124(12), 1330-6

Vincent A, Gahide G, Sportouch-Dukhan C, Covinhes A, Franck-Miclo A, Roubille F, Barrère C, Adda J, Dantec C, Redt-Clouet C, Piot C, Nargeot J, Barrère-Lemaire S (2012). Downregulation of the transcription factor ZAC1 upon PreC and PostC protects against ischemia-reperfusion in the mouse myocardium., Cardiovascular Research. 94(2), 351-358

Mesirca P, Alig J, Torrente AG,Muller JC, Marger L, Rollin A, Marquilly C, Vincent A, Dubel S, Bidaud I, Fernandez A, Seniuk A, Engeland B, Singh J, Miquerol L, Emke H, Eschenhagen T, Nargeot J, Wickman K, Isbrandt D, Mangoni ME (2014). Cardiac arrhythmia induced by genetic silencing of 'funny' (f) channels is rescued by GIRK4 inactivation, Nature Communications. 5(), 4664

Torrente AG, Mesirca P, Neco P, Rizzetto R, Dubel S, Barrere C, Sinegger-Brauns M, Striessnig J, Richard S, Nargeot J, Gomez AM, Mangoni ME (2016). L-type Cav1.3 channels regulate ryanodine receptor-dependent Ca2+ release during sino-atrial node pacemaker activity, Cardiovascular Research. 109(3), 451-461

Mesirca P, Bidaud I, Briec F, Evain S, Torrente AG, Le Quang K, Leoni AL, Baudot M, Marger L, Chung You Chong A, Nargeot J, Striessnig J, Wickman K, Charpentier F, Mangoni ME (2016). G protein-gated I KACh channels as therapeutic targets for treatment of sick sinus syndrome and heart block, PNAS. 113(7), E932-941

Vincent A, Sportouch C, Covinhes A, Barrère C, Gallot L, Delgado-Betancourt V, Lattuca B, Solecki K, Boisguérin P, Piot C, Nargeot J, Barrère-Lemaire S (2017). Cardiac mGluR1 metabotropic receptors in cardioprotection, Cardiovascular Research. 113(6), 644-655

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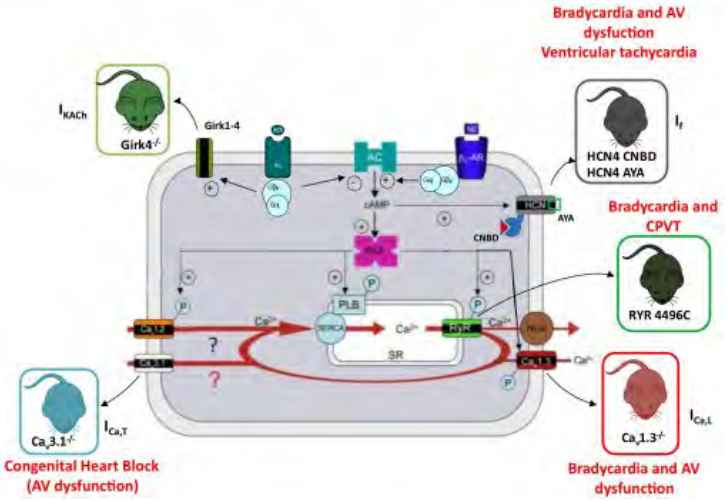
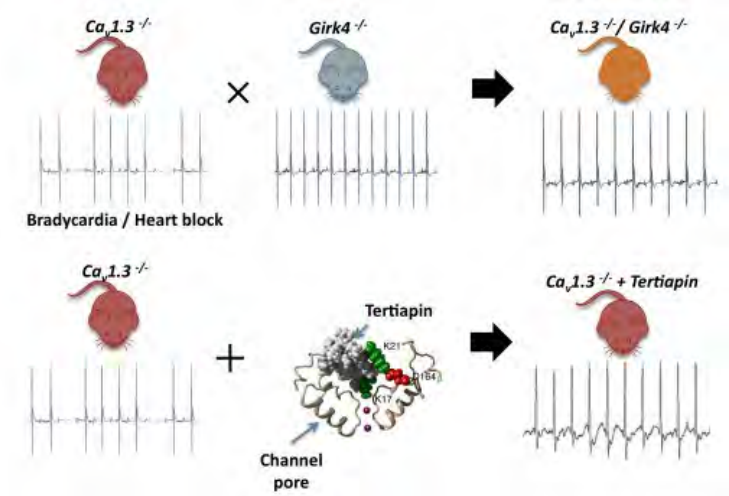
Mouse models of sino-atrial node dysfunction



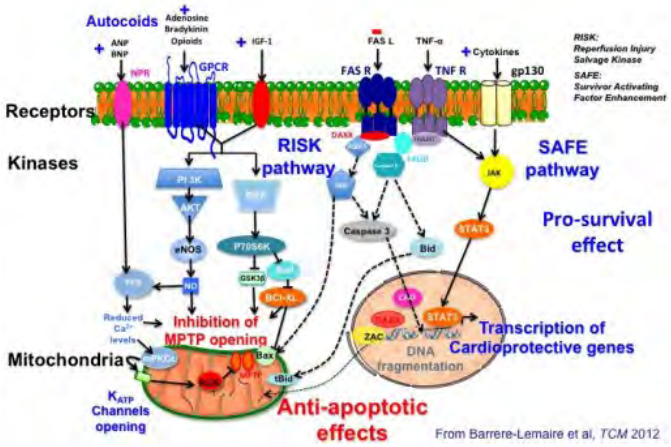
Mouse models of sino-atrial node dysfuction available in our research team. Models are generated by inducing constitutive or conditional loss-of-function in ion channels involved in the generation of sino-atrial pacemaker activity and atrioventricular conduction.

Targeting of GirK4 channels rescues sino-atrial dysfunction



Cav1.3 knockout (KO) mice show sinus bradycardia and 2nd degree atrioventricular block. Girk4 KO mice present with normal heart. Crossing these mouse lines produces Cav1.3/Girk4 KO animals with normal heart rate. When Cav1.3 KO mice undergo an intraperitoneal injection of the GIRK pore blocker tertiapin (represented bound to the channel pore) normalization of heart rate is observed. Girk4 targeting could be a future therapeutic approach for dysfunction of heart automaticity.

Cardioprotective cellular pathways to fight Ischemia-reperfusion injury



Our objective is to develop strategies that prevent cellular apoptosis following ischemia-reperfusion injury. We target the apoptotic extrinsic pathway down-stream the FAS receptor and stimulate the cardioprotective pathways.

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Sylvain Richard

Ion channels and Calcium Homeostasis in Cardiac and Vascular Muscles

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Jacques Mercier
Montpellier

Laboratory is superbly equipped for investigations ranging from in vivo function to molecular function with recognized experts in the fields of ion channels, Ca signaling, arrhythmias, pharmacology, cell biology, and biochemistry, with hospital facilities for translational research and human cells.

Key facts

Team

- Researchers : 6
- Technicians : 2
- Postdoc fellows : 2
- PhD Students : 4

Translational approaches

- Patents : 4
- Clinical research grants : 2
- Industry partnerships : 3

International research links

- UK
- Lebanon
- Brazil

Keywords

- Heart
- arrhythmias
- conduction disorders
- vascular tone
- hypertrophy
- contraction
- heart failure
- sodium handling
- calcium handling
- ion channels
- hypertension
- microelectrode
- patch-clamp
- Ca imaging
- electrophysiology

Biological Resources

- Rodent models: Heart failure with reduced/preserved ejection fraction; hypertrtophy, HTAP, Ischemia-reperfusion

Research Brief :

Thanks to complementary expertise in cellular and in vivo electrophysiology, pharmacology, functional imaging, and cell biology, we aim at identifying novel concepts and pharmacological targets in cardiovascular diseases (Figure 1). We study Excitation-Contraction coupling during heart failure (HF) where cardiac remodeling leads not only to pump failure but also to arrhythmias, including ventricular tachycardia/fibrillation responsible for sudden cardiac death (Figure 2). We focus on anti-arrhythmic drugs targeting ion channels, with emphasis on concepts integrating the role of intracellular Ca2+ and/or Na+ as major triggering factors. We add studies of molecular events determining HF progression, in relation with target systems (ion channels, Ca2+ handling, and neuro-hormonal/metabolic imbalances). Among different drugs currently studied, we seek to identify and understand the beneficial effects of neuroprostans. At the vascular level, we study the role of Na+ (Nav channels) and Ca2+ homeostasis in the contraction of vascular myocytes (VSMCs). We focus on hypoxia and mechanosensitivity, especially in hypertension and vasomotion. Another major axis of our research concerns intrinsic alterations of VSMCs exhibiting similarities with tumor cells in idiopathic PHA (Figure 3). Functional and genetic studies are carried out on cells from PHAi patients. These myocytes have high capacity for proliferation and resistance to senescence associated with telomeric stability.

- **Methodologies Used :**

Broad expertise and unique plat-form to study "from organ function in vivo to cell function". Wide range of biological models, techniques, methodologies.
Cardiac function, in vivo: Echographs: Vevo 3100 + Photoacoustic VisualSonics; ECG telemetry; Intracardiac exploration (Pressure/Volume; conduction).
Single cardiomyocytes & cell lines, hiPS, in vitro: Contraction, calcium (fluorescent dyes), electrophysiology; protein function ("channeling" activity).
Set-ups: 4 patch-clamp & 1 µelectrode (electrophysiology), 2 spectrofluorometry (Ionoptix, Fura-2 & Indo1) for Ca2+ measurements) and single cell contraction, 1 multi-photon laser scanning microscope & 1 confocal microscope.
Organ contraction (arteries: rodent, hamsters, human) ex vivo

Publications

Andre L, Boissière J, Reboul C, Perrier R, Zalvidea S, Meyer G, Thireau J, Tanguy S, Bideaux P, Hayot M, Boucher F, Obert P, Cazorla O, Richard S (2010). Carbon monoxide pollution promotes cardiac remodeling and ventricular arrhythmia in healthy rats., American journal of respiratory and critical care medicine. 181(6), 587-95

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http://u1046.edu.umontpellier.fr/annuaire/equipe-n1-responsable-sylvain-richard/

Figure 1

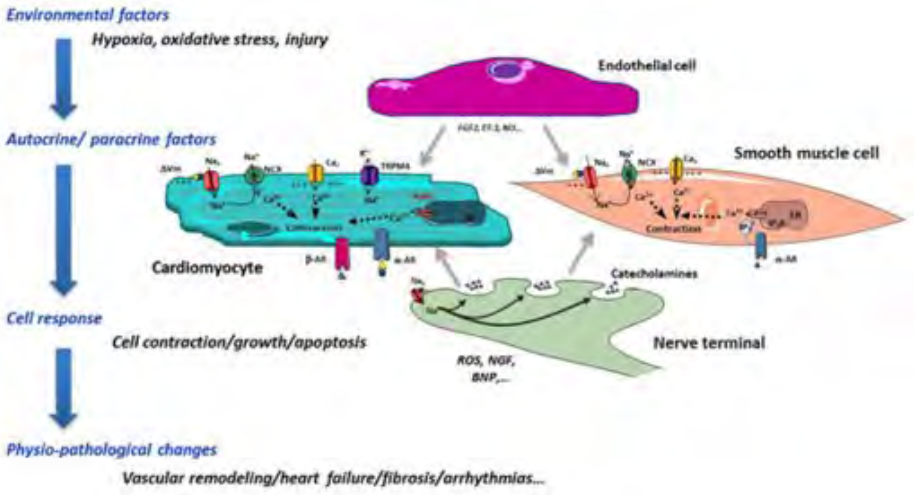


Figure 2

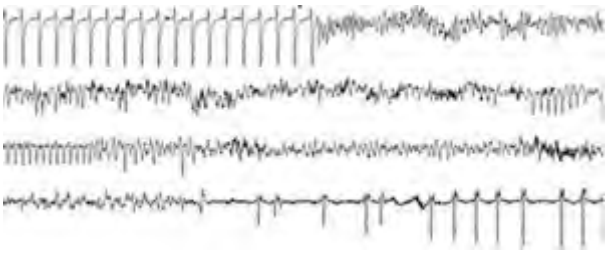
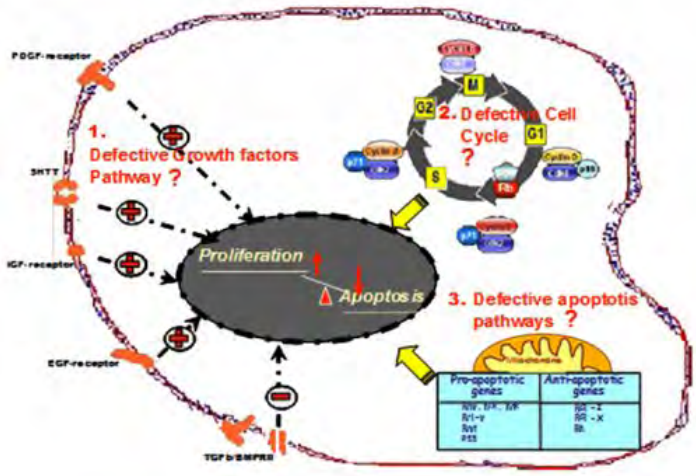


Figure 3



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http://u1046.edu.umontpellier.fr/annuaire/equipe-n1-responsable-sylvain-richard/

Key facts

Team

- Researchers : 5
- Technicians : 2
- Postdoc fellows : 2
- PhD Students : 2

Translational approaches

- Patents : 3
- Clinical research grants : 3
- Industry partnerships : 0

International research links

- Germany, Spain, Italy, Poland

Keywords

- clusterin
- Biomarkers
- Heart failure
- Cardiovascular cells
- Troponin
- Proteome
- MiRNAome
- phosphorylation
- Echocardiography
- O-GlcNAcylation

Biological Resources

- Plasma and serum biobanks (heart failure patients, myocardial infarction, abdominal aorta aneurysm)
- Macrophages and smooth muscle cells from patients with abdominal aorta aneurysm.
- Human aorta normal and diseased tissue biobank

Florence Pinet

Identification of molecular determinants of cardiovascular diseases

Université de Lille
Institut Pasteur de Lille UMR1167
Philippe Amouyel
Lille

Translational research involved in the search of potential biomarkers of cardiac diseases using differential "Omics" technologies :proteomic, miRNAomic

Research Brief :

The research project of our group is translational with the aim to find new biomarkers of left ventricular remodeling post-infarction and heart failure. The team has expertise on coordinating recruitment of patients with cardiac disorders, clearly phenotyped for left ventricular remodeling post-infarction (REVE 1 (n=266) and REVE 2 (n=246) studies) or heart failure (PTHF (n=60) and INCA (n>2000) studies. These clinical studies allow recuperating plasma and serum samples that are used for differential proteomic and transcriptomic (miRNA and lncRNA) analyses. We have developed techniques allowing access and detection of plasma ?deep? proteome. We have the expertise in discovery and validation of targets from proteomic (SELDI-TOF, 2D-DIGE, multiplex, ELISA) and miRNAomic (arrays, Q-RT-PCR). Two approaches are currently developed: 1) a clinical approach with the purpose to develop clinical diagnostic applications for which we analyzed all the data obtained by system biology and; 2) a molecular approach with the purpose to understand the mechanisms underlying the targets (proteins, post-translational modified proteins, miRNA, lncRNA) modulation in the pathologies studied. The discovery of new biological factors involved in the different cardiovascular pathologies would help to a better stratification of patients at risk.

- **Methodologies Used :**

Tissues, cells and plasma/serum (depleted for major proteins) proteomic.
2D-gel electrophoresis, SELDI-TOF, mass spectrometry
Arrays and Q-RT-PCR for miRNAs and lncRNAs, ELISA, multiplex assays
Primary culture of neonatal rat cardiomyocytes, human smooth muscle cells (aorta), macrophages
Laser-microdissection laser, cells and tissues imaging

Publications

Dubois E, Richard V, Mulder P, Lamblin N, Drobecq H, Henry JP, Amouyel P, Thuillez C, Bauters C, Pinet F (2011). Decreased serine207 phosphorylation of troponin T as a biomarker for left ventricular remodelling after myocardial infarction., European heart journal. 32(1), 115-23-9

Kumarswamy R, Bauters C, Volkmann I, Maury F, Fetisch J, Holzmann A, Lemesle G, Degroote P, Pinet F, Thum T (2014). The Circulating Long Non-Coding RNA LIPCAR Predicts Survival in Heart Failure Patients., Circulation research. 114(10), 1569-75

Dubois-Deruy E, Belliard A, Mulder P, Bouvet M, Smet-Nocca C, Janel S, Lafont F, Beseme O, Amouyel P, Richard V, Pinet F. (2015). Interplay between phosphorylation and O-N-acetylglucosaminylation of troponin T in ischaemic heart failure, Cardiovascular Research. 107(1), 56-65

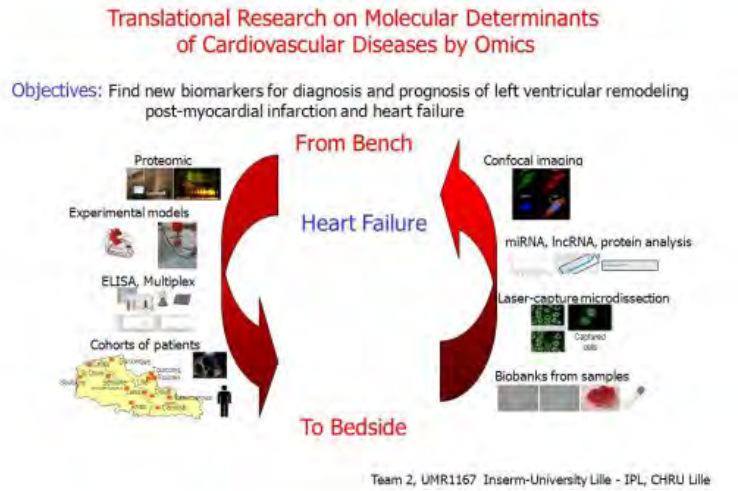
Gupta SK, Foinquinos A, Thum S, Remke J, Zimmer K, Bauters C, de Groote P, Boon R, de Windt L, Preissl S, Hein L, Batkai S, Pinet F, Thum T (2016). Preclinical development of a microRNA-based therapy for the infarcted heart of elderly individuals, Journal of the Americal College of Cardiology. 66(1), 1557-71

Pinet F, Cuvelliez M, Kelder T, Amouyel P, Radonjic M, Bauters (2017). Integrative network analysis reveals time-resolved mechanisms underlying left ventricular remodeling in post-myocardial infarction patients., BBA-Mol Bas Dis. 1863(6), 1445-1453

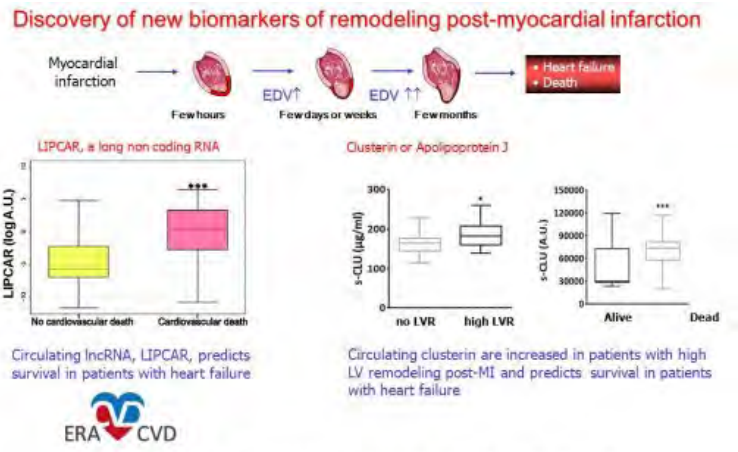
Turkieh A, Fertin M, Bouvet M, Mulder P, Drobecq H, Lemesle G, Lamblin N, de Groote P, Porouchani S, Chwastyniak M, Beseme O, Amouyel P, Mouquet F, Balligand JL, Richard V, Bauters C, Pinet F (2018). Expression and implication of clusterin in left ventricular remodeling after myocardial infarction, Circulation- Heart Failure. 11(6), e004838

Pinet Florence - florence.pinet@pasteur-lille.f r - 33 3 20 87 72 15 - http://www.pasteur-lille.fr/fr/recherche/u744/index.html

Activity of team 2

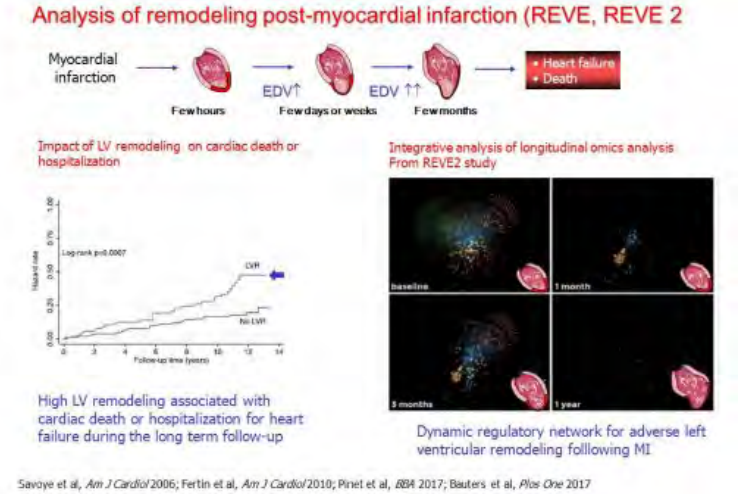


Major results in HF



Fertin et al, *Am J Cardiol* 2010; Kumarswamy et al, *Circ Res* 2014; Turkieh et al, *Circ Heart Failure* 2018

Major results in HF



Savoye et al, *Am J Cardiol* 2006; Fertin et al, *Am J Cardiol* 2010; Pinet et al, *BBA* 2017; Bauters et al, *Plos One* 2017

Pinet Florence - florence.pinet@pasteur-lille.f r - 33 3 20 87 72 15 - http://www.pasteur-lille.fr/fr/recherche/u744/index.html

Key facts

Team

- Researchers : 14
- Technicians : 11
- Postdoc fellows : 3
- PhD Students : 11

Translational approaches

- Patents : 4
- Clinical research grants : 1
- Industry partnerships : 1

International research links

- Europe
- United States

Keywords

- Intestine
- Circadian rhythm
- Adipose tissue
- Mitochondrial functions
- Transcriptional regulation
- Pharmacology
- Nuclear receptors
- Metabolic syndrome
- Liver
- Biochemistry
- Pharmacology
- Molecular biology
- Genetically-modified mice
- Cellular biology
- Mouse phenotyping

Biological Resources

- Animal tissues (from our different mouse models)
- Human biopsies (liver and adipose tissue)

Bart Staels

Nuclear receptors in the metabolic syndrome

Université de Lille 2 (Droit
et Sante)
Institut Pasteur de Lille UMR 1011 Inserm - CHU de Lille UMR 1011
Bart Staels
Lille

We combine a strong background in the field of nuclear receptors and metabolism, and a unique scientific environment and up-to-date technological platforms.

Research Brief :

The organism senses its energy status through the close communication of several organs which integrate multiple endocrine (hormones, cytokines) and metabolic (glucose, free fatty acids..) signals. Dysregulation of the tight control of metabolism leads to dyslipidemia, insulin resistance and obesity which predispose to the development of cardiovascular complications and atherosclerosis. We aim to better understand the metabolic functions of nuclear receptors (NRs), with a major focus on FXR, PPARs, Rev-erba and RORa, and to define the potential benefit of pharmacological agents acting via these NRs on human health.
The role of these NRs will be investigated by comparing total- or organ-specific deficient or over-expressing mice of these NRs to wild-type mice with respect to basal metabolic parameters, energy expenditure, gene and protein expression and pharmacological response. Cellular and molecular approaches will also be used to identify the molecular mechanisms at the basis of the identified physiological functions. Since NRs are potential pharmacological targets, the use of existing as well as the identification of novel synthetic ligands will allow us to study the biological effects of these compounds. Finally, the role of these NRs in human physiology will be investigated by analysis of tissue biopsies from subjects suffering from metabolic disorders. It is expected that these approaches will uncover new therapeutic strategies for the treatment of metabolic diseases.

- **Methodologies Used :**

In vivo mouse phenotyping, Cell culture (cell lines or primary cells), Molecular biology approaches (transfection, quantitative PCR, Western-blot, Chromatin Immunoprecipitation (ChIP), Gene silencing, DNA micro-array technology, ChIP-seq technology?), Immuno-histochemistry

Publications

Staels B, Rubenstrunk A, Noel B, Rigou G, Delataille P, Millatt LJ, Baron M, Lucas A, Tailleux A, Hum DW, Ratziu V, Cariou B, Hanf R (2013). Hepatoprotective effects of the dual peroxisome proliferator-activated receptor alpha/delta agonist, GFT505, in rodent models of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis., Hepatology (Baltimore, Md.). 58(6), 1941-52

Woldt E, Sebti Y, Solt LA, Duhem C, Lancel S, Eeckhoute J, Hesselink MK, Paquet C, Delhaye S, Shin Y, Kamenecka TM, Schaart G, Lefebvre P, Nevière R, Burris TP, Schrauwen P, Staels B, Duez H (2013). Rev-erb-alpha modulates skeletal muscle oxidative capacity by regulating mitochondrial biogenesis and autophagy., Nature medicine. 19(8), 1039-46

Montaigne D, Marechal X, Coisne A, Debry N, Modine T, Fayad G, Potelle C, El Arid JM, Mouton S, Sebti Y, Duez H, Preau S, Remy-Jouet I, Zerimech F, Koussa M, Richard V, Neviere R, Edme JL, Lefebvre P, Staels B (2014). Myocardial contractile dysfunction is associated with impaired mitochondrial function and dynamics in type 2 diabetic but not in obese patients., Circulation. 130(7), 554-64

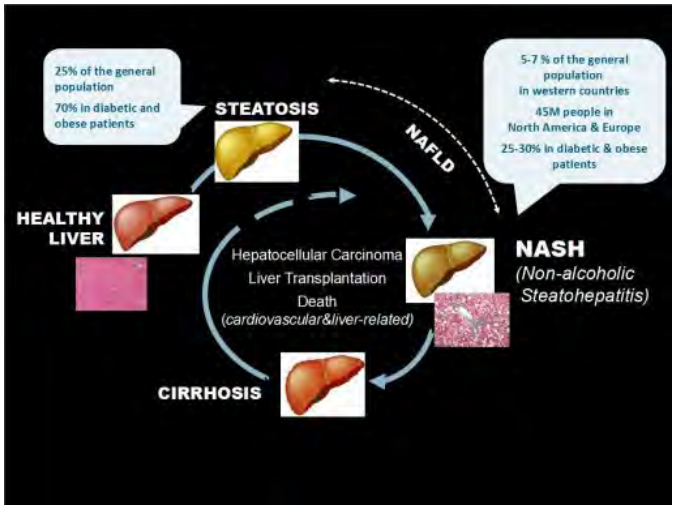
Francque S, Verrijken A, Caron S, Prawitt J, Paumelle R, Derudas B, Lefebvre P, Taskinen MR, Van Hul W, Mertens I, Hubens G, Van Marck E, Michielsen P, Van Gaal L, Staels B. (2015). PPARalpha gene expression correlates with severity and histological treatment response in patients with non-alcoholic steatohepatitis., Journal of Hepatology. 63(1), 164-73

Trabelsi MS, Daoudi M, Prawitt J, Ducastel S, Touche V, Sayin SI, Perino A, Brighton CA, Sebti Y, Kluza J, Briand O, Dehondt H, Vallez E, Dorchies E, Baud G, Spinelli V, Hennuyer N, Caron S, Bantubungi K, Caiazzo R, Reimann F, Marchetti P, Lefebvre P, Bäckhed F, Gribble FM, Schoonjans K, Pattou F, Tailleux A, Staels B, Lestavel S. (2015). Farnesoid X receptor inhibits glucagon-like peptide-1 production by enteroendocrine L cells., Nature Communications. 6(), 7629

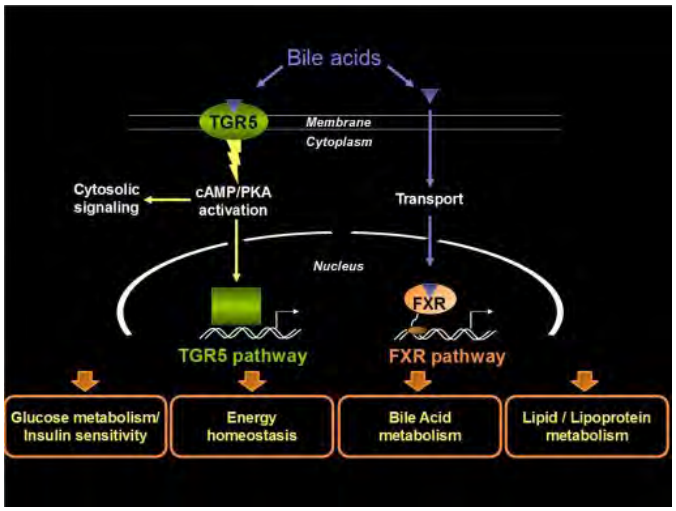
Briand O, Touche V, Colin S, Brufau G, Davalos A, Schonewille M, Bovenga F, Carrière V, de Boer JF, Dugardin C, Riveau B, Clavey V, Tailleux A, Moschetta A, Lasunción MA, Groen AK, Staels B, Lestavel S. (2016). Liver X receptor regulates triglyceride absorption through intestinal down-regulation of scavenger receptor class B, type 1., Gastroenterology. 150(3), 650-8

Staels Bart - Bart.Staels@pasteur-lille.fr - 03-20-87-78-25 - http://www.u1011.lille.inserm.fr/

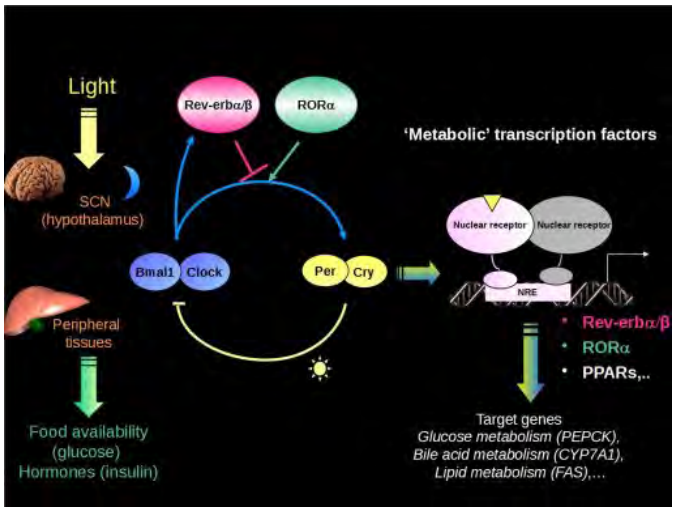
Non-Alcoholic Fatty Liver Disease (NAFLD): modulation by PPARs



Bile acids signal via FXR and TGR5



Transcriptional control of metabolic pathways by circadian oscillators



Staels Bart - Bart.Staels@pasteur-lille.fr - 03-20-87-78-25 - http://www.u1011.lille.inserm.fr/

Research teams with secondary association to PMN Institute

Key facts

Team

• Researchers : 5
• Technicians : 1
• Postdoc fellows : 2
• PhD Students : 4

Translational approaches

• Patents : 0
• Clinical research grants : 2
• Industry partnerships : 6

International research links

• USA , China, Spain

Keywords

• Viral cardiac infection
• Inflammation
• Persistence
• Physiopathology
• CVB3 induced myocarditis in mice model
• Human cardiac cell infection

Biological Resources

• Cardiac tissue collection from patients with acute or chronic cardiomyoapathies

LAURENT ANDREOLETTI

Cardiovir

Université de Reims
Champagne-Ardenne
Université EA4684
LAURENT ANDREOLETTI
REIMS

The research is original at the national and international levels, both in the fields of heart viral diseases and enterovirus infections. In France, there are only two research groups involved in enterovirus persistent infections and with its will and effort to study these infections in humans.

Research Brief :

Human enteroviruses (EVs), and specifically Coxsakievirus B (CVB), are a common cause of acute cardiac infection and myocarditis in children and young adults. In 10% of the cases, the acute infection evolves to persistence, inducing a chronic myocarditis. This pathology will lead in 9% of the patient to a dilated cardiomyopathy (DCM 7 cases/100 000 inhabitants), which is the second leading cause of cardiac transplantation. The involvement of these forms in DCM is supported by the detection of viral RNA and VP1 capsid protein in 35% of the cardiac samples of end stage patient suffering from idiopathic myocarditis. Molecular mechanisms triggering the switch from the acute to the chronic myocarditis and DCM are still unknown, therefore limiting the development of specific therapeutic strategies against EV-induced chronic heart diseases. A better understanding of the molecular mechanisms implicated in EV persistence of viral forms in human cardiac tissues and could stimulate the development of new therapeutic strategies in acute and chronic cardiac infections, such as DCM, caused by EV.

• **Methodologies Used :**

We used for the first time a new technology allowing broad viral detection in clinical samples that couples
broad-range PCR amplification to electrospray ionization-time of flight mass spectrometry analysis (PCRMS).
We developed NGS approaches to quantify major and minor persistent viral population in heart tissues.
We developed an original CVB3 induced chronic myocarditis in DBA/2J mice model.

Publications

Lévêque N, Renois F, Talmud D, Nguyen Y, Lesaffre F, Boulagnon C, Bruneval P, Fornes P, Andréoletti L (2012). Quantitative genomic and antigenomic enterovirus RNA detection in explanted heart tissue samples from patients with end-stage idiopathic dilated cardiomyopathy., J Clin Microbiol. 50(10), 3378-80

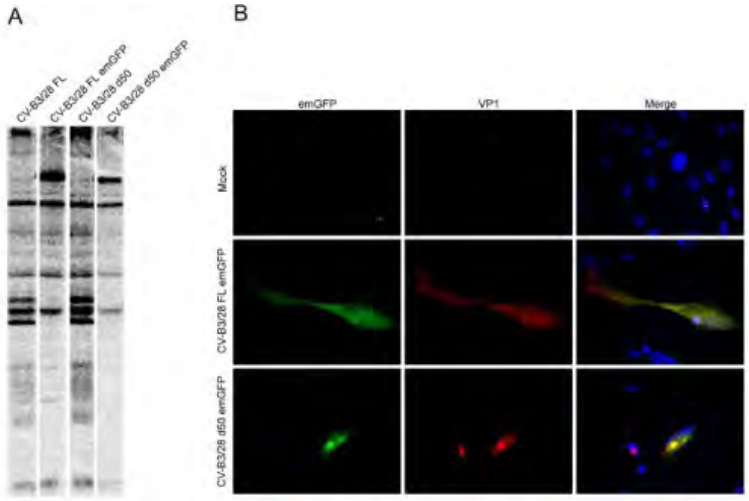
Nguyen Y, Renois F, Lévêque N, Giusti D, Picard-Maureau M, Bruneval P, Fornes P, Andreoletti L. (2013). Virus detection and semiquantitation in explanted heart tissues of idiopathic dilated cardiomyopathy adult patients by use of PCR coupled with mass spectrometry analysis. J, J Clin Microbiol. 51(07), 2288-94

Ashrafpoor G, Andréoletti L, Bruneval P, Macron L, Azarine A, Lepillier A, Danchin N, Mousseaux E, Redheuil A. (2013). Fulminant human herpesvirus 6 myocarditis in an immunocompetent adult: role of cardiac magnetic resonance in a multidisciplinary approach., Circulation.. 128(23), e445-7

Bouin A, NGuyen Y, Wehbe M, Renois F, Fornes P, Bani-Sadr F, Andreoletti L (2016). Major Persistent 5? Terminally Deleted Coxsackievirus B3 Populations in Human Endomyocardial Tissues., Emerg Infect Dis. 22(8), 1488-90

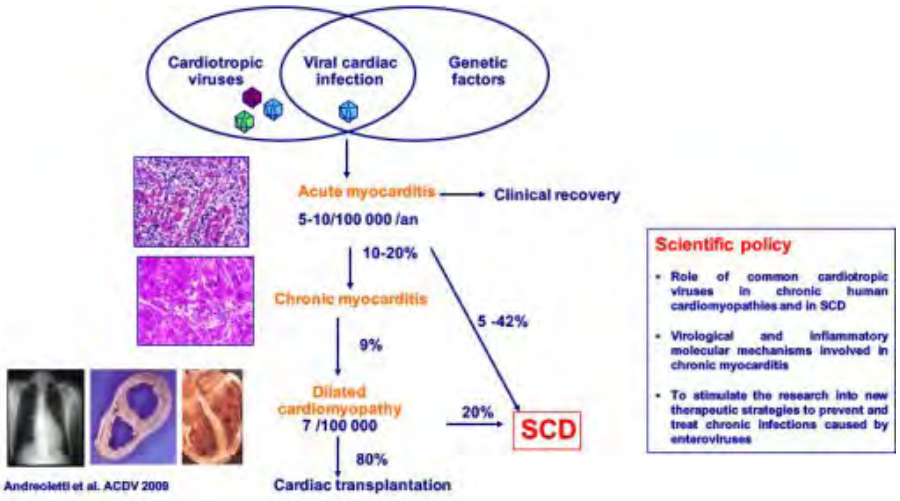
Wehbe M, Huguenin A, Lévêque N, Semler BL, Hamze M, Andreoletti L, Bouin A. (2016). Construction of a subgenomic CV-B3 replicon expressing emerald green fluorescent protein to assess viral replication of a cardiotropic enterovirus strain in cultured human cells, J Virol Methods.. 230(3), 1-6

Expression of viral proteins of 5' deleted viral forms



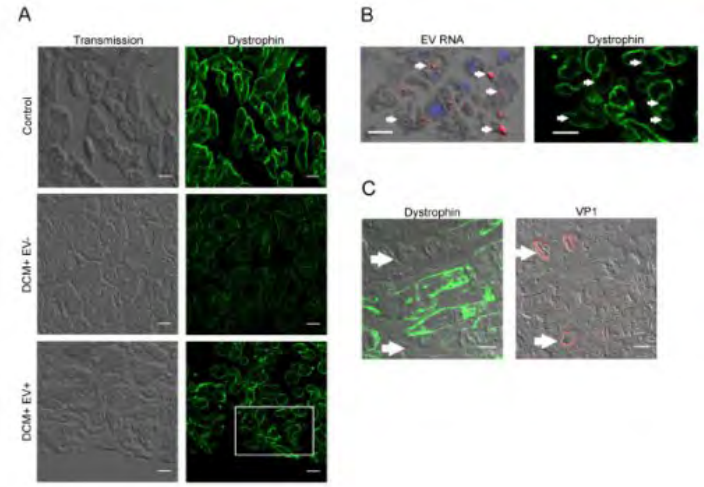
A. In vitro translation assay of CV-B3 replicons B. Transfection of FL and deleted viral RNA carrying emGFP into HCM. Cells were fixed 24H and immunofluorescent assays were performed. Blue: Nucleus, Red: VP1, Green: emGFP.

Pathophysiology of viral cardiac infection



Andreoletti et al. ACDV 2009

Impact of EV B persistence on dystrophin



A. Immunofluorescent staining of dystrophin in the heart tissue sections of infected DCM patients (DCM+ EV+), uninfected EV DCM patients (DCM+ EV-) and controls (DCM- EV-). Bar scale=50?m. The white rectangle is displayed in B. B. Serial sections of cardiac tissues of infected DCM patients (DCM+ EV+) were analyzed by in situ hybridization of the viral RNA (left, blue: nucleus, red: RNA) and immunofluorescent staining of dystrophin (right, green).

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http://www.univ-reims.fr/universite/organisation/organisation,7741,18258.html?&args=FZpTBCx4A55ycboVAsLr4egEs1m_s60YHWOGlggT4HdZVVISMEfCz5Y

Hemostasis

Pascale Gaussem

Innovatives Therapies in Haemostasis IThEM

Faculté de Pharmacie de Paris Université de Paris 05
(Université Rene Descartes)
Inserm UMR-S1140 CHU Paris
Pascale Gaussem
Paris

Key facts

Team

• Researchers : 10
• Technicians : 6
• Postdoc fellows : 1
• PhD Students : 9

Translational approaches

• Patents : 3
• Clinical research grants : 5
• Industry partnerships : 5

International research links

• USA, Netherlands, Italy, China, Mexico, Poland, Greece, Germany, Canada, UK, Switzerland, belgium, Spain, Brazil, Argentina

Keywords

• endothelium
• signalling
• platelets
• antithrombotic agents
• vasculogenesis
• cell culture
• genetics
• preclinical model
• thrombosis
• biochemistry

Biological Resources

• human and animals adult stem cells (rat, mouse, rabbit)
• human and animals tissus (biopsy)
• human cord blood
• human and animal peripheral blood (rat, mouse, rabbit)
• DNA and RNA banks from cardiovascular disease
• cohorts : Venous thrombosis (FARIVE), pulmonary fibrosis (COFI)

UMR_S1140 is recognized for its expertise in haemostasis, in management of antithrombotic treatments and in development of innovative biotherapies (in vitro platelet and vascular cell production).

Research Brief :

The main mission of UMR_S1140 is to develop new therapeutic strategies in haemostasis and cardiovascular diseases through the improvement of knowledge in the field of molecular mechanisms of haemostasis and vasculogenesis, and of management of antithrombotic drugs to notably decrease drug-related adverse events, with strong clinical application potential.
Our scientific objectives are:
i) to understand the role of adult stem cells with vasculogenic properties in blood vessel formation in physiological conditions and in lung and cardiovascular diseases, and to analyse the haemocompatibility in mechanical circulatory/respiratory support (Theme 1),
ii) to address novel strategies to produce platelets and analyse new mechanisms involved in the regulation of platelet functions and to conduct a transversal program on antithrombotic agents from the molecular basis of coagulation to animal models and clinical studies in targeted populations (Theme 2).

• **Methodologies Used :**

Preclinical models of angiogenesis, thrombosis, bleeding, and intravital microscopy
Cell biology: cell culture in 2D and 3D scaffold (primary (endothelial), stem cells(endothelial progenitors, megacaryocytes,mesenchymal), cell transfection, in vitro angiogenesis assays, flow experiments, immunocytochemistry, production of recombinant proteins
Molecular biology, RT-qPCR, Flow cytometry, biochemistry (WB, ELISA, signalling)
Immunohistochemistry, confocal microscopy...

Publications

Silvestre JS, Smadja DM, Lévy BI (2013). Postischemic revascularization: from cellular and molecular mechanisms to clinical applications., Physiological reviews. 93(4), 1743-802

JOURDI G, SIGURET V, MARTIN AC, GOLMARD JL, GODIER A, SAMAMA CM, GAUSSEM P, GOUIN-THIBAULT I, LE BONNIEC B (2015). Association rate constants rationalise the pharmacodynamics of apixadan and rivaroxaban, Thromb Haemostas. 114(1), 78-86

GODIER A, TAYLOR G, GAUSSEM P (2015). Inefficacy of platelet transfusion to reverse ticagrelor, N Engl J Med.. 372(2), 196-7

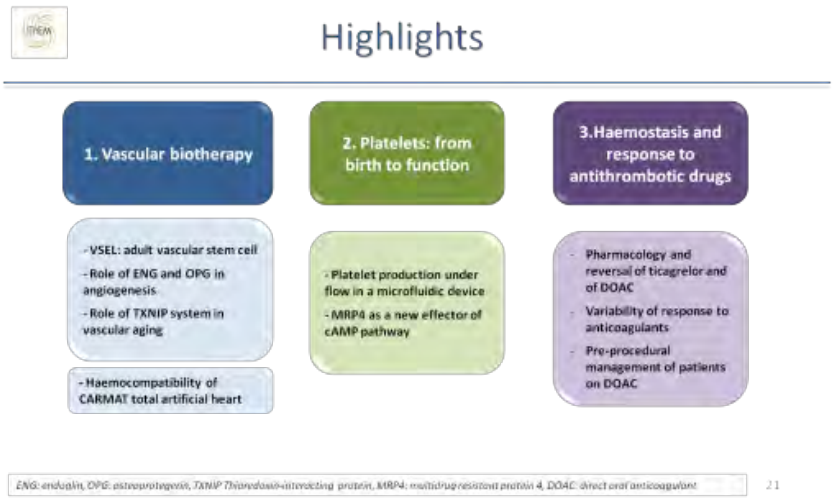
DECOUTURE B, DREANO E, BELLEVILLE-ROLLAND T, KUCI O, DIZIER B, BAZAA A, COQUERAN B, LOMPRE AM, DENIS CV, HULOT JS, BACHELOT-LOZA C, GAUSSEM P* (2015). Impaired platelet activation and cAMP homeostasis in MRP4-deficient mice., Blood. 126(15), 1823-30*

SMADJA DM, SAUBAMÉA B, SUSEN S, KINDO M, VAN BELLE E, BRUNEVAL P, JANSEN P, ROUSSEL JC, LATRÉMOUILLE C, CARPENTIER A. (2017). Bioprosthetic total artificial heart induces a profile of acquired hemocompatibility with membranes recellularization, J Am Coll Cardiol. 70(3), 404-6

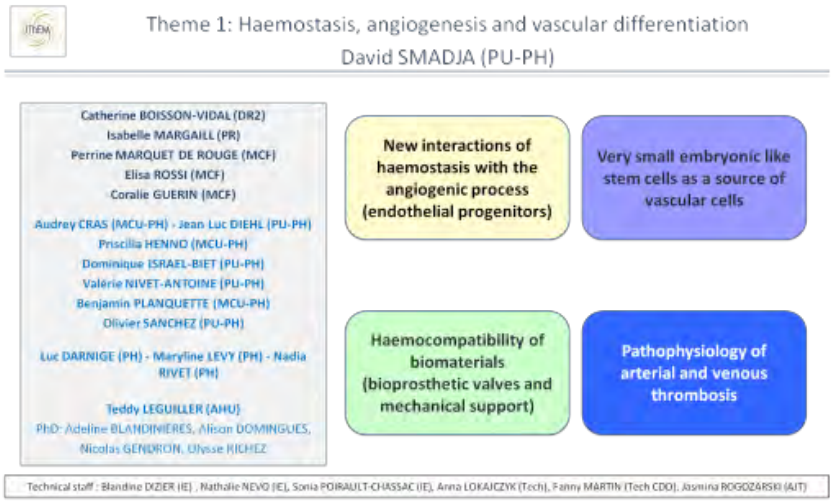
GODIER A, DINCQ AS, MARTIN AC, RADU A, LEBLANC I, ANTONA M, VASSE M, GOLMARD JL, MULLIER F, GOUIN-THIBAULT I. (2017). Predictors of pre-procedural concentrations of direct oral anticoagulants: a prospective multicentre study., Eur Heart J. 38(31), 2431-39

Gaussem Pascale - pascale.gaussem@parisdescartes .fr - +33153739939 - http://www.ithem.fr

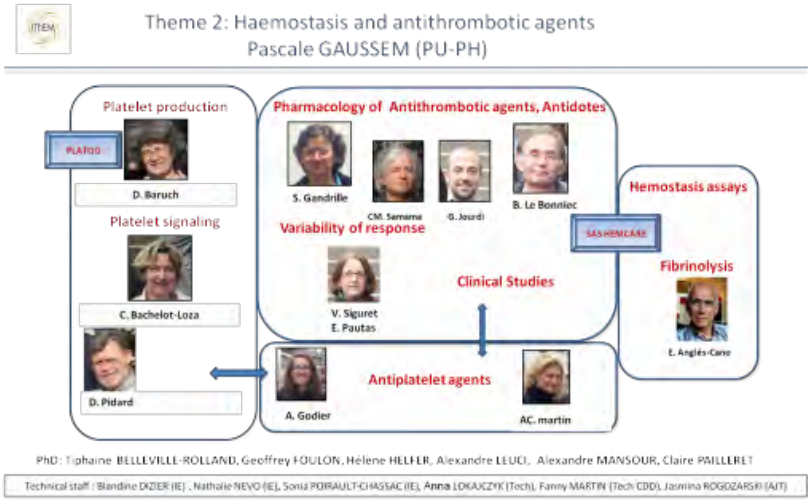
UMR-S1140 highlights



Work force and research of Theme 1



Work force and research of Theme 2



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DENIS Cécile

Integrative hemostasis: from fundamental aspects to hemorrhagic disorders

Université Paris Sud : Paris 11
Inserm UMR1176
Denis Cécile
Le Kremlin-Bicêtre

Our team strength resides in the integrative approach applied to the study of hemostatic proteins with techniques ranging from enzymology to the use of dedicated murine models and patients samples.

Key facts

Team

- Researchers : 9
- Technicians : 5
- Postdoc fellows : 4
- PhD Students : 2

Translational approaches

- Patents : 6
- Clinical research grants : 0
- Industry partnerships : 3

International research links

- Canada
- Germany

Keywords

- Coagulation
- Platelets
- Bleeding disorders
- Von Willebrand factor
- Hemophilia
- Murine models
- Biochemistry

Biological Resources

- Von Willebrand disease mouse models
- Macrophage specific LRP1-deficient mice
- Hemophilia A murine model
- Inducible Factor X-deficient mice

Research Brief :

The research portfolio of the team is tailored around the patho-physiological aspects of haemostasis, with particular emphasis on hemorrhagic disorders related to coagulation and platelet defects. Four main topics can be distinguished: 1) pathogenesis of congenital or acquired von Willebrand disease (VWD); 2) pathogenesis of hemophilia; 3) pathogenesis of (inherited) platelet disorders; 4) role of VWF beyond hemostasis.
In general, these topics are addressed in a similar fashion: there is a focus on fundamental & clinical aspects of the disease, we further delineate clearance pathways of hemostatic proteins, and novel therapeutic strategies are explored and tested in in vivo models. For instance, we continue to focus on the pathology of VWD-type 2B. Recently, we identified that VWD-type 2B results in an unexpected thrombocytopathy, while an increased clearance of VWF/platelet complexes plays a role in the thrombocytopenia that characterizes these patients. By using in vitro & in vivo approaches we are deciphering the molecular basis of these findings. Furthermore, we use our mouse model for hemophilia A to get more insight into the functional defects that is associated with several mutations in factor VIII. This model is also be used to test a series of candidates that might be useful for the specific treatment of patients with mild/moderate hemophilia A. We also continue our work on filaminopathy A as a cause of platelet dysfunction.

• Methodologies Used :

In vivo thrombosis models in mice
Platelet function analysis
Culture of CD34+ cells
Bleeding assays in mice (tail clip assay, tail vien transection)
Surface Plasmon Resonance (Octet)
Coagulation assays/ Thrombin Generation Time
Hydrodynamic injection
Stable cell transfection
Immunofluorescence staining (Classic or Duo-link)
Perfusion assays in flow
ELISA
Production and purification of recombinant proteins

Publications

Casari C, Berrou E, Lebret M, Adam F, Kauskot A, Bobe R, Desconclois C, Fressinaud E, Christophe OD, Lenting PJ, Rosa JP, Denis CV, Bryckaert M (2013). von Willebrand factor mutation promotes thrombocytopathy by inhibiting integrin ?IIb?3, Journal of Clinical Investigation. 123(), 5071-5081

Casari C, Du V, Wu Y-P, Kauskot A, De Groot PG, Christophe OD, Denis CV, De Laat B, Lenting PJ. (2013). Accelerated uptake of VWF/platelet complexes in macrophages contribute to VWD-type 2B associated thrombocytopenia., Blood. 122(), 2893-2902

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Kauskot A, Poirault-Chassac S, Adam F, Muczynski V, Aymé G, Casari C, Bordet JC, Soukaseum C, Rothschild C, Proulle V, Pietrzyk-Nivau A, Berrou E, Christophe OD, Rosa JP, Lenting PJ, Bryckaert M, Denis CV, Baruch D (2016). LIM kinase/cofilin dysregulation promotes macrothrombocytopenia in severe von Willebrand disease-type 2B, JCI Insight. 1(16), e88643

Elaïb Z, Adam F, Berrou E, Bordet JC, Prévost N, Bobe R, Bryckaert M, Rosa JP (2016). Full activation of mouse platelets requires an ADP secretion pathway regulated by SERCA3 ATPase-dependent calcium stores., Blood. 128(), 1129-1138

Muczynski V, Aymé G, Regnault V, Vasse M, Borgel D, Legendre P, Bazaa A, Harel A, Loubière C, Lenting PJ, Denis CV, Christophe OD. (2017). Complex formation with pentraxin-2 regulates factor X plasma levels and macrophage interactions., Blood. 129(), 2443-2454

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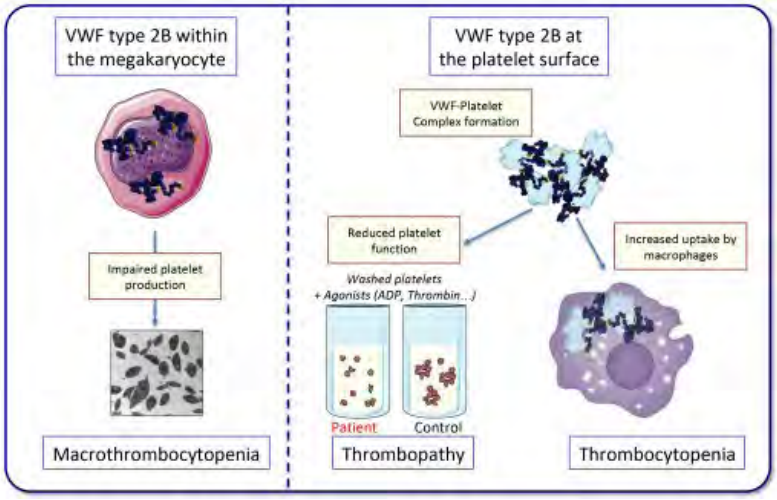
Mechanims of thrombopathy and thrombocytopenia induced by a mutation in von Willebrand factor



Von Willebrand disease type 2B (VWD-type 2B) is a pathological condition in which gain-of-function mutations in the plasma protein von Willebrand factor (VWF) lead to a bleeding rather than a prothrombotic phenotype. Underlying molecular mechanisms involve: 1) defective platelet function due to impaired signaling leading to lack of activation of alphaIIbbeta3 integrin and 2) thrombocytopenia originating from a central production defect as well as from an increased clearance of platelets.

Blood cover February 2016, volume 127, issue 6

CD115+-derived macrophages from wild-type C57BL/6 mice were incubated with human coagulation factor X (FX). Cells were then immunostained for human FX (green), while nuclei and polymerized actin were counterstained using 4?,6-diamidino-2-phenylindole (blue) and Alexa 647-labeled phalloidin (magenta), respectively. Images were acquired using widefield microscopy, original magnification ×63. Article by Muczynski et al, page 778.

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Pneumology

Key facts

Team

• Researchers : 17
• Technicians : 8
• Postdoc fellows : 1
• PhD Students : 7

Translational approaches

• Patents : 1
• Clinical research grants : 0
• Industry partnerships : 1

International research links

• Europe, Singapour, United States, Canada

Keywords

• Cell plasticity
• Respiratory diseases (CF, COPD, Carcinoma)
• Airway epithelium biology
• Epithelial-mesenchymal transition
• Epithelium remodeling
• Cell culture
• Cell biology
• Cell imaging

Biological Resources

• Human tissues from lungs and nose
• Cohorts of CF and COPD patients
• Biocollection of airway epithelial cells and lung tissues
• In vitro/in vivo models of epithelium regeneration and epithelial cell migration
• Primary cultures of airway epithelial cells

Myriam Polette

Plasticity of the airway epithelium in normal and pathological conditions

Université de Reims
Champagne-Ardenne
Inserm UMR-S 1250
Myriam POLETTE
Reims

Combine biological and clinical approaches to identify predictive or severity-associated biomarkers of respiratory diseases and to test novel therapeutic strategies to restore a functional airway epithelium

Research Brief :

The plasticity of the airway epithelium plays a major role in inflammatory diseases such as chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF) as well as in cancers. The hallmark of these chronic inflammatory respiratory diseases is the transdifferentiation of epithelial cells leading to an epithelial remodeling: basal and secretory cell hyperplasia, squamous metaplasia, alteration of ciliated cell differentiation. Epithelium remodeling prevents the restoration of the epithelial functional integrity. In addition, inflammation maintains epithelial remodeling, which eventually leads to severe and irreversible respiratory insufficiencies. These abnormalities of epithelial repair can also promote the genesis of pre-neoplastic and neoplastic lesions. In this context, dedifferentiation processes associated with an epithelial-mesenchymal transition are involved in the metastatic progression of Non-Small-Cell Lung Carcinoma (NSCLC) and Head and Neck Cancer (HNC). We recognized two research axes to investigate cell plasticity: epithelial transdifferentiation in the remodeling of the airway epithelium in CF and COPD; epithelial dedifferentiation in the tumor progression of NSCLC and HNC. The two main objectives: (1) to identify the molecular actors impacting respiratory diseases among the ones involved in epithelial cell differentiation and functionality; (2) to correlate these actors to the severity of the pathology and propose consistent therapeutic solutions.

• **Methodologies Used :**

Cell models
Cell and molecular biology
Microscopy (Video, confocal, calcium signaling,...)
Histology and immunohistochemistry

Publications

Marcet B, Chevalier B, Luxardi G*, Coraux C*, Zaragosi E, Cibois M, Robbe-Sermesant, Jolly T, Cardinaud B, Moreilhon C, Giovannini-Chami L, Nawrocki-Raby B, Birembaut P, Waldmann R, Kodjabachian L, Barbry P (2011). Control of vertebrate multiciliogenesis by miR-449 through direct repression of the Delta/Notch pathway, Nat Cell Biol. 13(6), 693-9*

Bonnomet A, Syne L, Brysse A, Feyereisen E, Thompson EW, Noël A, Foidart JM, Birembaut P, Polette M, Gilles C (2012). A dynamic in vivo model of epithelial-to-mesenchymal transitions in circulating tumor cells and metastases of breast cancer, Oncogene. 31(33), 3741-53

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Deslée G, Mal H, Dutau H, Bourdin A, Vergnon JM, Pison C, Kessler R, Jounieaux V, Thiberville L, Leroy S, Marceau A, Laroumagne S, Mallet JP, Dukic S, Barbe C, Bulsei J, Jolly D, Durand-Zaleski I, Marquette CH (2016). Lung volume reduction treatment vs usual care in patients with severe emphysema The REVOLENS randomized clinical trial, JAMA. 315(2), 175-84

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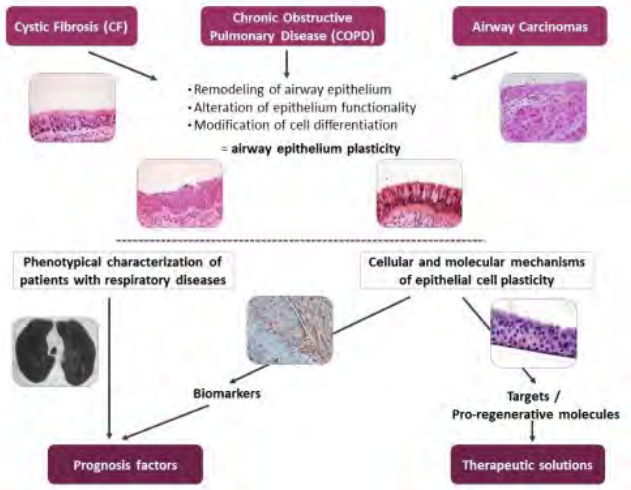
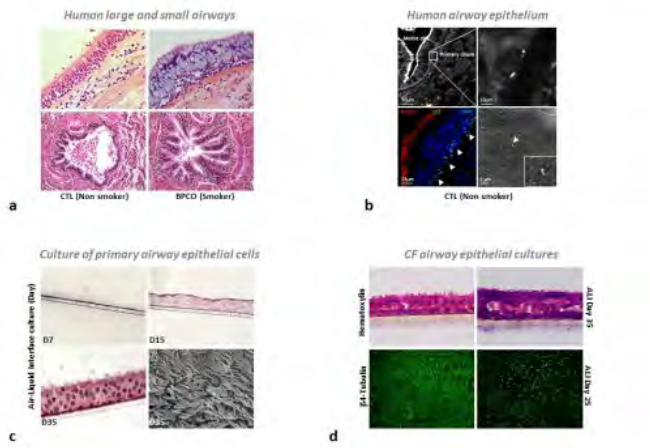
Research strategies

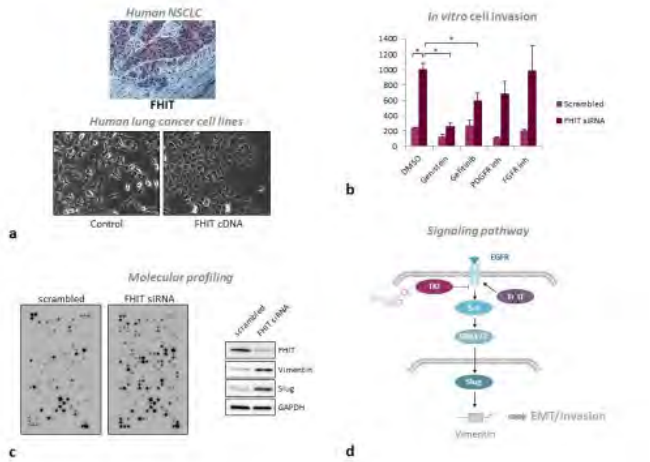


Airway epithelium remodeling and ciliogenesis alteration in CF and COPD



a. Histological sections showing goblet cell hyperplasia (up) and narrowing of small airways (bottom) in COPD. b. Detection of primary cilia in basal cells in normal or remodeled epithelium. c. Successive steps of human airway epithelial regeneration in an in vitro model of air-liquid interface culture. d. CF epithelial cells reconstitute in vitro a remodeled epithelium, higher and exhibiting ciliated cell differentiation default.

FHIT maintains an epithelial phenotype in lung cancer cells



a. Loss of FHIT expression in invasive lung cancer cells (up); FHIT overexpression in invasive lung cancer cells restores an epithelial phenotype (bottom). b. FHIT silencing induces expression of EMT-associated genes. c. FHIT-regulated tumor invasion is RTK dependent. d. EMT induced by FHIT inhibition requires an EGFR signaling pathway.

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Gilles Lalmanach

Proteolytic mechanisms in inflammation

Université François
Rabelais Tours
Inserm UMR1100
Mustapha Si-Tahar
Tours

Key facts

Team

• Researchers : 10
• Technicians : 2
• Postdoc fellows : 0
• PhD Students : 5

Translational approaches

• Patents : 2
• Clinical research grants : 2
• Industry partnerships : 2

International research links

• Voir le lien: https://cepr.inserm.univ-tours.fr/equipes-/equipe-inserm-2-br-g-lalmanach/collaborations-internationales/

Keywords

• COPD, Fibrosis
• inflammation
• Protease inhibitor
• Protease
• Lung
• Enzymology
• Protein Chemistry
• Cell Biology
• Signaling pathways

Biological Resources

• Collection of sputa from patients with COPD (GOLD1 to GOLD4)
• Annotated collections of frozen lung tissues and derivatives
• Anima model of COPD (+/- exacerbation)

Unique expertise in France in the field of proteolysis. At the crossroads of fundamental/basic sciences and translational clinical approaches.

Research Brief :

Major research axes developed within the team are:

1- Role of pulmonary proteases in inflammatory pathologies:
(a) Regulation of the protease-antiprotease balance in idiopathic pulmonary fibrosis (IPF) and chronic obstructive pulmonary disease (COPD)
(b) Proteolytic regulation of proteins/peptides involved in the innate immunity
(c) Structure-function relationships of neutrophil serine proteases (NSPs), macrophage cysteine cathepsins and kallikrein-related proteinases
(d) Role of proteases in the epithelial?mesenchymal transition (EMT) and in the epithelial integrity
(e) Role of proteases in BM and ECM remodeling

2 - Control of the proteolytic activity in inflammatory pulmonary pathologies
(a) Targeting of NSPs and cysteine cathepsins
(b) Design of pseudopeptidic and biosynthetic analogs of protease inhibitors
(c) Imaging of proteolysis: activity-based probes

• **Methodologies Used :**

- Biochemical analyses (enzymology, peptide design, etc ...)
- Cellular analyses (signaling pathways, etc...)
- Biological analyses (biopsies, tissues, various biological fluids)
- Animal models of human pathologies

Publications

I. E. Valverde, F. Lecaille, G. Lalmanach, V. Aucagne & A. F. Delmas (2012). A biologically active bis-triazolo analogue of cystatin A through successive peptidomimetic alkyne/azide ligations., Angew. Chem. Int. Ed. (),

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Team "Proteolytic mechanisms in inflammation"

Team "Proteolytic mechanisms in inflammation"CEPR/Inserm U100/University of Tours (January 2018)

Bernard Mari

Non coding genome & lung disorders

Université de Nice - Sophia
Antipolis
CNRS UMR 7275
Jean-Louis Nahon
Sophia-Antipolis

Key facts

Team

- Researchers : 4
- Technicians : 1
- Postdoc fellows : 1
- PhD Students : 3

Translational approaches

- Patents : 2
- Clinical research grants : 0
- Industry partnerships : 2

International research links

- Germany, Belgium, USA

Keywords

- Non-coding RNA
- Lung
- Cancer
- Fibrosis
- Hypoxia
- Functional Genomics
- Gene Editing
- Biochemistry
- Bioinformatics

Developing RNA therapeutics and biomarkers for lung diseases

Research Brief :

Our team explores the potential function of several non-coding RNAs whose expression is deregulated in several lung disorders. Controlling the expression of some of these RNAs may likely provide important opportunities for the development of powerful new therapeutic strategies. Our research is strongly associated to the Pulmonology & Thoracic Oncology department of the University Hospital of Nice (Pr. C-H Marquette & Dr S. Leroy, AIR project) and is affiliated to the hospital-university federation (FHU) OncoAge. Our research mainly focuses on two axes :

- Exploration of miRNAs as therapeutic targets and prognosis biomarkers in idiopathic pulmonary fibrosis (IPF).

- Identification of non-coding RNAs (miRNAs & LncRNAs) associated with lung cancer aggressiveness, in particular in adaptation to a hypoxic environment.

Methodologies Used :

Functional genomics - Molecular Biology - CRISPR/Cas9 - Bioinformatics - Biochemistry - Animal models

Publications

Bertero, T., Gastaldi, C., Bourget-Ponzio, I., Mari, B., Meneguzzi, G., Barbry, P., Ponzio, G., and Rezzonico, R. (2013). CDC25A targeting by miR-483-3p decreases CCND-CDK4/6 assembly and contributes to cell cycle arrest., Cell Death Differ. 20(), 800

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Bertero, T., Rezzonico, R., Pottier, N., and Mari, B. (2017). Impact of MicroRNAs in the Cellular Response to Hypoxia, Int Rev Cell Mol Biol. 333(), 91

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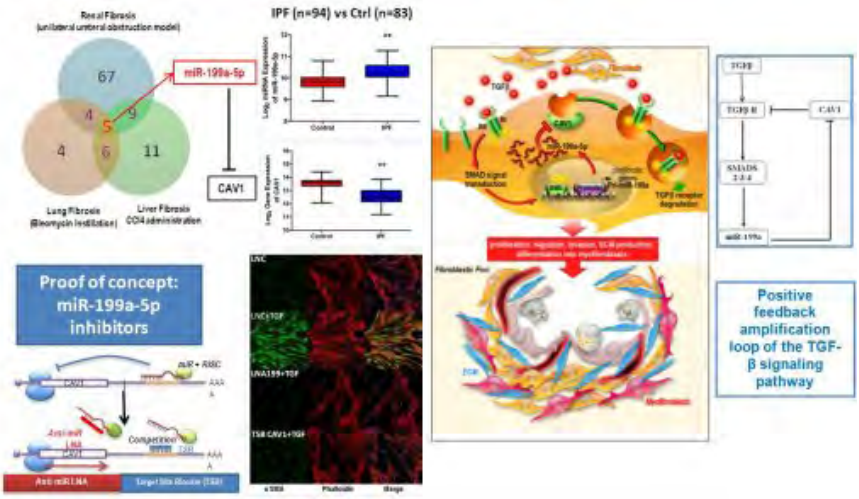
Main goals

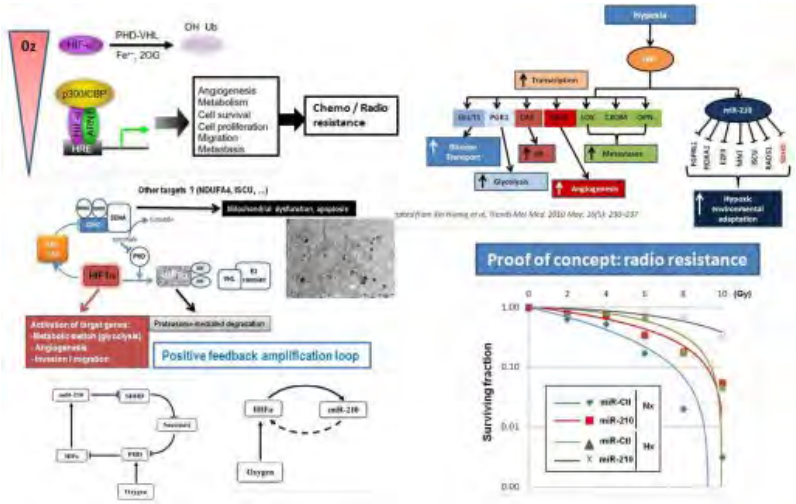
Fundamental Aspects:
Deciphering ncRNAs target gene networks and mode of action

Clinical Aspects:
Developing RNA therapeutics and prognosis tools

miR-199a-5p is a TGF-beta rheostat & promotes myofibroblast differentiation & pulmonary fibrosis



The master hypoxamiR miR-210 acts as a regulator of the hypoxic response in Lung Tumor cells



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INSTITUT MONDOR DE RECHERCHE BIOMÉDICALE

Sophie Lanone

Respiratory effects of environmental contaminants

UPEC
Inserm UMR955
Jorge Boczkowski
Créteil

Unique approach based on pluridisciplinary expertise comprising MDs (lung specialists - general population and occupational medicine - and lung pathologist) as well as PhDs (in cellular and molecular biology, biochemistry, respiratory physiology).

Key facts

Team

- Researchers : 9
- Technicians : 3
- Postdoc fellows : 2
- PhD Students : 4

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 0

International research links

- Japan
- Germany
- Canada

Keywords

- Lung remodeling
- COPD
- Cigarette smoke
- Environmental agressors
- Senescence
- Human samples
- Preclinical models
- Cell culture
- Lung function
- Cell and tissue imagery

Biological Resources

- P16 KO mice
- Atg5-LysMCre mice
- COPD patients lung fibroblasts

Research Brief :

Environmental assault, whether occupational or not, play a central role in the etiology of several respiratory diseases, such as Chronic Obstructive Pulmonary Disease (COPD). This represents a true public health issue, especially as news particular contaminants, nanoparticles (NP), arise those later years, accompanied by incompletely characterized effects on health. Overall, our team is interested in studying the respiratory consequences of environmental particle inhalation, with a particular focus on 1/the role of cellular senescence in the physiopathology of post-tobacco and/or occupational COPD; 2/ the respiratory consequences of exposure to anthropic NP, seeking a link between physico-chemical properties of NP and their biological effects on lungs; and 3/ early origins of COPD and other respiratory consequences to environmental exposure (nanoparticle of anthropic origin, air pollution, ...)

- **Methodologies Used :**

Human samples (lung tissue, blood, bronchoalveolar lavage, ...)
Cell culture (primary, cell lines - human and mice)
Development of preclinical models (cigarette smoke exposure, nanoparticle exposure, exposure to complex realistic atmospheres...)
Lung function evaluation
Senescence and autophagy pathways investigation
Synchrotron-based X-ray microfluorescence

Publications

Dagouassat M, Gagliolo JM, Chrusciel S, Bourin MC, Duprez C, Caramelle P, Boyer L, Hue S, Stern JB, Validire P, Longrois D, Norel X, Dubois-Randé JL, Le Gouvello S, Adnot S, Boczkowski J. (2013). The cyclooxygenase-2-prostaglandin E2 pathway maintains senescence of chronic obstructive pulmonary disease fibroblasts., Am. J. Respir. Crti. Care Med.. 187(7), 703

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Andujar P, Courbon D, Bizard E, Marcos E, Adnot S, Boyer L, Demoly P, Jarvis D, Neukirch C, Pin I, Thabut G, Boczkowski J, Leynaert B. (2018). Smoking, telomere length and lung function decline: a longitudinal population-based study., Thorax. 73(), 283

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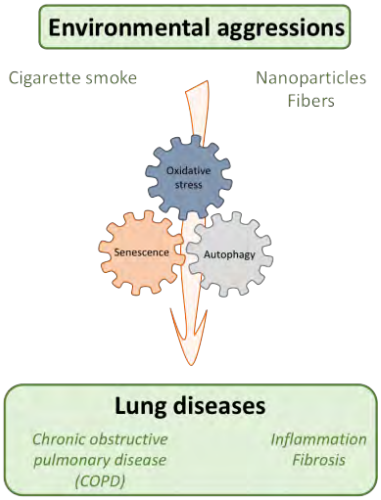
Global approach



Global approach developed by the team to study the respiratory consequences of environmental agressions

Lanone Sophie - sophie.lanone@inserm.fr - http://www.imrb.inserm.fr/equipes/s-lanone/

Key facts

Team

• Researchers : 8
• Technicians : 2
• Postdoc fellows : 3
• PhD Students : 0

Translational approaches

• Patents : 1
• Clinical research grants : 6
• Industry partnerships : 3

Keywords

• Asthma
• Airway inflammation
• Airway remodeling
• Lung transplantation
• Bio-markers
• Cohorts
• Primary human respiratory cells
• Mouse models
• Cell functions
• Immunodetections

Biological Resources

• Cohort of patients undergoing lung transplantation: clinical data and biological samples
• Ex vivo cultured human bronchial epithelial cells from asthmatics, from patients with COPD and from lung transplant recipients
• Ex vivo cultured airway smooth muscle cells from patients with asthma
• Murine models of asthma and of bronchiolar epithelium injury and repair
• Cohorts of patients with asthma and chronic obstructive pulmonary disease (COPD): clinical data and biological samples

Marina Pretolani

Airway inflammation and remodeling in chronic obstructive lung diseases

Université Paris Diderot Paris
7 UFR de Médecine
Inserm U1152
Marina Pretolani
Paris

> ***Multidisciplinarity know-how, i.e., from human biological material from patient cohorts to hands-on experience in primary-cultured human normal and diseased pulmonary cells and in vivo mouse models***

Research Brief :

The research developed by this Team is focused on the identification of novel molecular mechanisms involved in airway remodeling in severe asthma. Specifically, projects were aimed at positioning the airway epithelium and the airway smooth muscle (ASM) as fundamental elements of airway remodeling involved in asthma severity and progression and as potential new targets for therapeutics. Thus, this Team deciphers the cellular and molecular mechanisms involved in normal epithelium repair in vivo and examines specific epithelium alterations that may contribute to sub-epithelial fibrosis seen in severe asthma. In parallel, the mechanisms underlying ASM enlargement in severe asthma and the clinical benefit of bronchial thermoplasty, an endoscopic procedure that targets primarily this structure, are investigated. Studies are also undertaken to characterize novel severe asthma phenotypes, based mainly on differential expression of innate immune and T helper responses, and on more wide technologies (eg RNAseq, proteomic).
Finally, this Team studies the risk factors and the mechanisms involved in epithelium-mediated acute and chronic allograft dysfunctions in lung transplantation.
Overall, these studies are conducted using biological samples and clinical data from the multicenter longitudinal French COhort of BRonchial obstruction and Asthma (COBRA) that is managed by this Team and from patients undergoing lung transplantation at the Bichat Hospital (approximately 50 per year).

• **Methodologies Used :**

- culture of normal and diseased primary bronchial epithelial cells and airway smooth muscle cells from human biopsy and lung specimens
- Functional studies on isolated cells (differentiation, proliferation, migration, repair, activation)
- In vivo models of chronic asthma and of bronchiolar epithelium injury and repair in mice
- Identification of markers of interest in biological fluids (Luminex/Elisa, proteomic) and in cells and tissues (immunohistochemistry/immunofluorescence, confocal microscopy, flow cytometry)
- bio-statistical and biological approaches on human cohorts

Publications

Debray MP, Dombret MC, Pretolani M, Alavoine L, Thabut G, Brillet PY, Taillé C, Khalil A, Chanez P, Aubier M. (17). Early CT modifications following bronchial thermoplasty in patients with severe asthma., Eur Respir J. 15(49), 3-8

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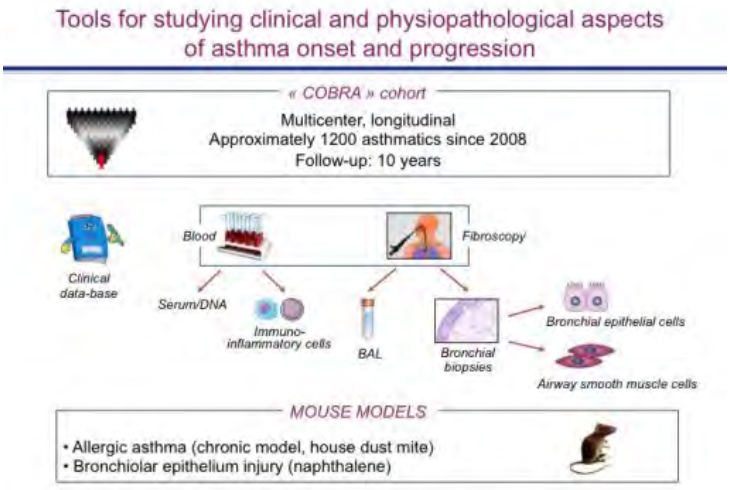
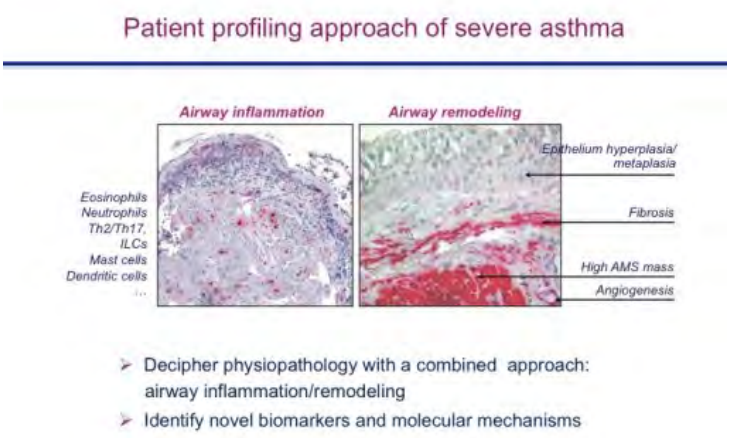
Tools for studying clinical and physiopathological aspects of asthma onset and progression



Studies on asthma are based on the use of the multicenter, longitudinal COBRA cohort. This cohort provides extensive information concerning natural history, biological and risk factors involved in disease onset, progression and response to treatment. It is also an important source of biological samples required for mechanistic studies and for setting-up proof-of-concept trials to test novel therapeutic tools.
Abbreviation : BAL, bronchoalveolar lavage

Patient profiling approach of severe asthma



Severe asthma is an heterogeneous disease, manifesting in several distinct clinical and histological phenotypes that develop through a variety of physiopathological mechanisms. A better characterization of these different phenotypes involves the use of wide panels of hallmarks of inflammation and remodeling, the characterization of cellular and molecular mechanisms involved in these processes, as well as the identification of novel biomarkers of disease onset and progression.

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Key facts

Team

• Researchers : 4
• Technicians : 2
• Postdoc fellows : 1
• PhD Students : 1

Translational approaches

• Patents : 2451467
• Clinical research grants : 0
• Industry partnerships : 0

International research links

• Great Britain, United States, Canada, Germany

Keywords

• immunity inflammation lung infection bacteria virus nanoparticles adenovirus
• PCR ; nanoparticles ;FACS ;cell culture ; in vivo lung experimental procedures

Jean-Michel Sallenave

Innate Immunity and anti-infective pulmonary defenses

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Marina Pretolani
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We are interested in the molecular and cellular mechanisms involved in pathogen (eg viruses such as Influenza, bacteria such as Pseudomonas aeruginosa) recognition and in the response to environmental and manufactured agents (i.e nanoparticles).

Research Brief :

It is now accepted that lung mucosal tissue confer important properties to the immune system, both at homeostasis and during infectious situations. At the mucosal surface, epithelial cells and alveolar macrophages interact, eg through surfactant, regulatory cytokines and antimicrobial molecules, to ensure a non-inflammatory regulatory and tolerogenic phenotype. After infection, this brake is released, and these cells participate in the network to organize pro-inflammatory responses and adaptive immunity to contain microbial aggression and to insure return to haemostasis. Our group is particularly interested in the innate mechanisms of defense and its dysregulation, which could explain the pathophysiology of lung chronic and acute inflammatory disorders.
Our main models of study focus on two aspects :
A) a therapeutic one, which aims to understand the basic mechanisms of host reponses against:
1) Pseudomonas aeruginosa infections, an opportunistic pathogen in nosocomial infections, as well as in cystic fibrosis and in exacerbations of chronic obstructive pulmonary diseases (COPD).
2) Lung infections by Influenza virus, a pathogen responsible for acute infections leading to seasonal flu or pandemic episodes, but also present during exacerbations in asthma, cystic fibrosis, COPD or lung fibrosis.
B) a prophylactic one, which aims to increase immune responses against these pathogens, by choosing adjuvant formulations able to break the mucosal tolerogenic milieu.

• **Methodologies Used :**

-PCR
-cell culture
-FACS
-ELISA
-PAGE analysis and Western Blot
-in vivo injections and instillation techniques (lung)
-immunological techniques

Publications

Motta JP, Magne L, Descamps D, Rolland C, Squarzoni-Dale C, Rousset P, Martin L, Cenac N, Balloy V, Huerre M, Fröhlich LF, Jenne D, Wartelle J, Belaaouaj A, Mas E, Vinel JP, Alric L, Chignard M, Vergnolle N, Sallenave JM (2011). Modifying the protease, antiprotease pattern by elafin overexpression protects mice from colitis., Gastroenterology. 140(4), 1272-82

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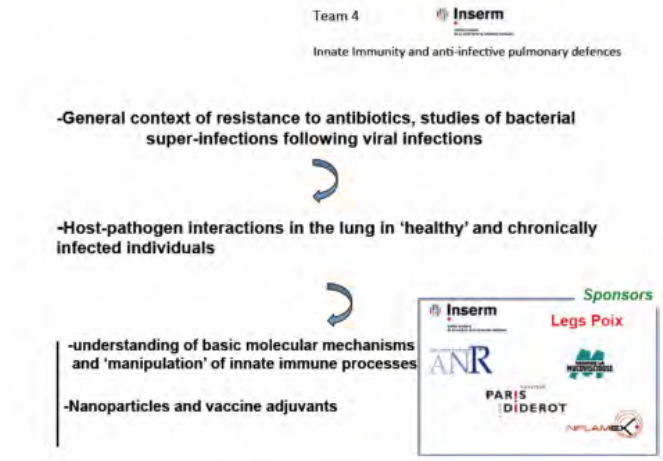
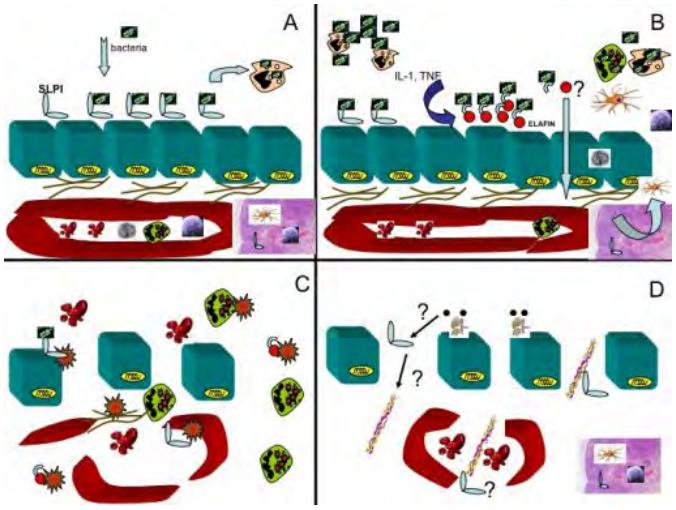
Team research interests



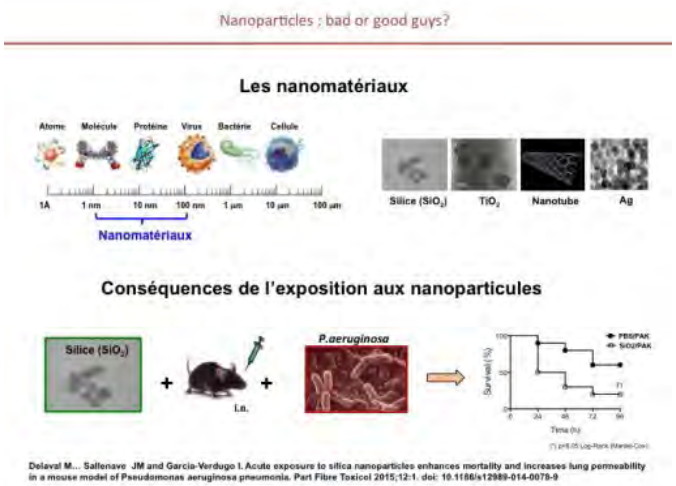
General themes and research interests of our team

Antimicrobial expression and functions at the lung mucosal interface



A)The lung alveolar-capillary barrier at haemostasis : antimicrobial molecules (AMMs, SLPI, elafin) are protective against infections and provide a tolerogenic phenotype at local lymph nodes. B)During infection, AMM expression increases in epithelial cells and generate chemotactic signals for inflammatory cells C)When the alveolar-capillary barrier is disrupted, AMM can protect tissue destruction with their anti-protease activity. D)AMMs are also important for tissue repair.

Nanoparticles as modulators of lung infections



Nanoparticles can influence/modulate lung responses towards infections. Our team is deciphering the molecular and cellular mechanisms by which nanoparticles (silica, silver...) can modulate the lung responses against bacteria (Pseudomonas aeruginosa...) and viral (Influenza) infectious agents.

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Key facts

Team

- Researchers : 4
- Technicians : 1
- Postdoc fellows : 6
- PhD Students : 5

Translational approaches

- Patents : 4
- Clinical research grants : 5
- Industry partnerships : 2

International research links

- Europe, United States of America, Canada, Japan, Israel and Australia.

Keywords

- Pulmonary vascular remodeling
- Nationwide web-based Registry
- Novel therapies
- Pulmonary Hypertension
- Inflammation
- Cell culture
- Flow cytometry
- Experimental models
- Tissue bank
- Cell and tissue fluorescent microscopy

Marc HUMBERT Olivier SITBON

Pulmonary Arterial Hypertension: Pathophysiology and Novel Therapies

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HUMBERT Marc
Le Plessis-Robinson

On the basis of a nationwide Registry, a unique biobank, experimental models and highly competitive scientists, our group focuses on molecular pathways causing pulmonary vascular remodeling, identifying targets to foster drug development and tests novel treatments for Pulmonary Hypertension (PH).

Research Brief :

Pulmonary arterial hypertension (PAH) describes a group of devastating diseases, comprising idiopathic and associated forms, causing breathlessness, loss of exercise capacity and death due to elevated pulmonary artery pressure and subsequent right heart failure. PAH is defined by an elevation of the mean pulmonary artery pressure above 25mmHg at rest without elevation of the pulmonary capillary wedge pressure. Extensive pulmonary artery remodeling with loss of vessel patency is the underlying pathomechanism. The main scope of our Research Team relates to PAH pathophysiology and clinical management. Deciphering of the mechanisms of lung vascular remodeling and identification of novel molecular targets to alleviate and ultimately cure PAH is the main objective of this proposal. Our group will study a number of molecular pathways causing pulmonary vascular remodeling in human and animal models of pulmonary hypertension (PH) on the basis of a nationwide web-based Registry, a biobank, and highly competitive scientists: Dr Sylvia COHEN-KAMINSKY, Dr Christophe GUIGNABERT, Dr Alice HUERTAS, Dr Frédéric PERROS, and the medical and surgical team of the Referral Center for PH at Bicêtre Hospital (AP-HP) and Hôpital Marie Lannelongue. Our main goal is to identify targets for therapy, foster drug development based on these targets and test novel treatments in order to alleviate and cure PAH, a large burden to mankind.

- **Methodologies Used :**

System flow cytometry MacsQuant
EnVision 2103 plate reader
FlexStation 3
Q-PCR system in real time StepOne +
PCR thermal cyclers
ChemiDoc system multiple detection: fluorescence, colorimetry, densitometry, chemiluminescence
Nanodrop
Electrophysiology
Microscopy
Laser Microdissection Microscope
Hypoxia chambers for rodents
Hemodynamic laboratory for rodents

Publications

Humbert M, Lau EM, Montani D, Jaïs X, Sitbon O, Simonneau G. (2014). Advances in therapeutic interventions for patients with pulmonary arterial hypertension., Circulation. 130(24), 2189-208

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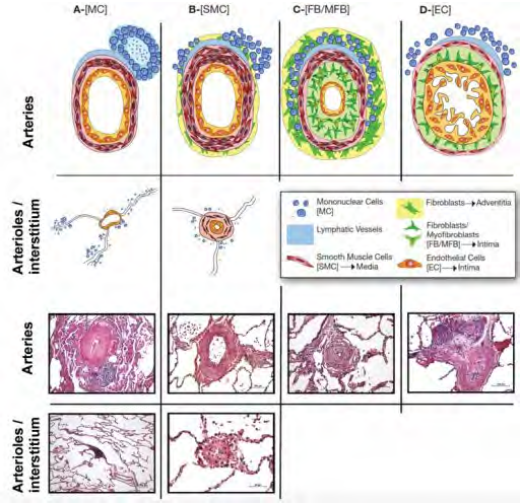
Typical histologic lesions encountered in lungs from patients with Pulmonary Arterial Hypertension



(A) Tertiary lymphoid tissue (top); interstitial inflammatory infiltrates (bottom). (B) Hypertrophy/hyperplasia of the media; perivascular lymphocytic infiltrates (top); Fibrosis of the adventitia (bottom). (C) Concentric intimal fibrosis (nonlaminar or laminar); fibroblasts and myofibroblasts accumulation, combined with hypertrophy of the media and fibrous broadening of the adventitia and perivascular inflammation. (D) Plexiform lesions.

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Key facts

Team

- Researchers : 12
- Technicians : 2
- Postdoc fellows : 2
- PhD Students : 8

Translational approaches

- Patents : 2
- Clinical research grants : 0
- Industry partnerships : 4

Keywords

- asthma pathophysiology
- Airway smooth muscle
- clinical research
- cell biology
- molecular biology
- imaging

Biological Resources

- Cohorts of patients
- human lung tissue
- animal models of asthma and COPD

Patrick Berger

Bronchial remodeling

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Inserm U1045
Marthan Roger
Bordeaux

The project of the team associates human and animal studies in a multidisciplinary approach (physiologists, chest physicians, radiologists, physicists, pharmacologists, and paediatricians) with strong interconnection between the team and the clinical investigation center in the hospital

Research Brief :

Asthma and chronic obstructive pulmonary disease (COPD) are very frequent inflammatory diseases that are characterized by different patterns of bronchial remodelling. However, characteristics and localization of the increased in Bronchial Smooth Muscle (BSM) mass are different. In COPD, there is a BSM cell hypertrophy which is only present in distal bronchi whereas in asthma, there are both BSM cell hypertrophy and hyperplasia within the entire bronchial tree. Anyhow, BSM remodelling has been associated with a poor prognosis, high morbidity, and deterioration of lung function. As a consequence BSM remodelling should be a target of innovative treatments.

The general aim of this project is therefore to understand, evaluate and treat bronchial remodelling. The specific aims are to further unravel the mechanisms of bronchial remodelling in both asthma and COPD as well as to develop new non invasive tools to assess bronchial remodelling in vivo.

• Methodologies Used :

For this purpose, the research project will combine clinical, functional, radiological data obtained in vivo with histological, functional, cellular, and molecular data obtained in vitro.

Publications

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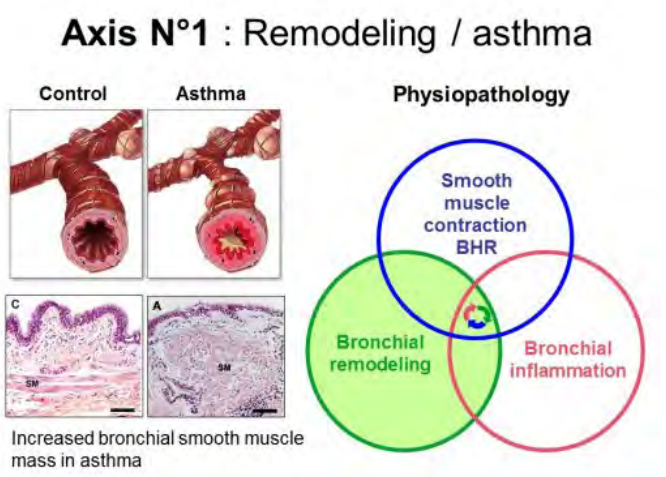
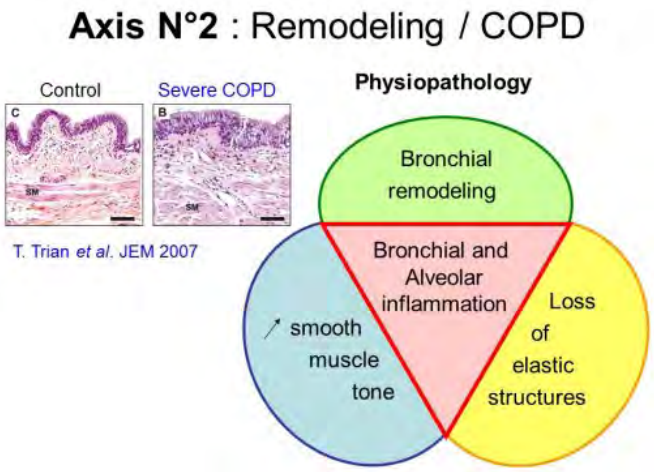
Axis 1



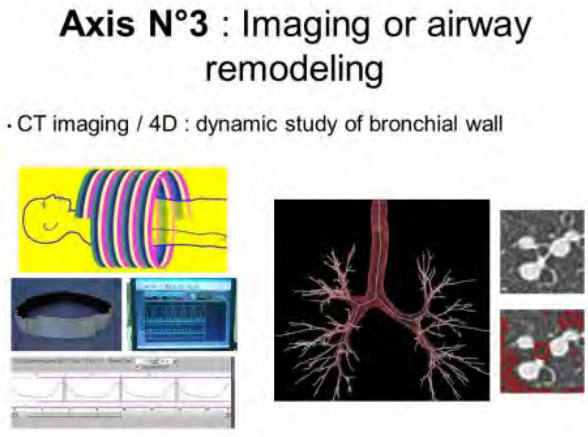
Bronchial remodeling in asthma

Axis 2



Bronchial remodeling in COPD

Axis 3



Imaging of bronchial remodeling

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Key facts

Team

• Researchers : 2
• Technicians : 2
• Postdoc fellows : 2
• PhD Students : 3

Translational approaches

• Patents : 1
• Clinical research grants : 0
• Industry partnerships : 2

International research links

• Laboratory of cell physiology - Brussels - Belgium - Pr P. Gailly
• Robert M. Berne Cardiovascular Research Center - Charlottesville, USA - Dr B. Isakson

Keywords

• Pulmonary hypertension
• Vascular remodeling
• Calcium signaling
• Vascular reactivity
• Airborne pollution
• Patch-clamp
• Chronic hyperoxia
• Chronic hypoxia
• Fluorescent imaging

Biological Resources

• Rats and mice with chronic hypoxic pulmonary hypertension (with the use of a hypobaric chamber)
• Rat model of idiopathic pulmonary hypertension (a single injection of monocrotaline)
• Rat model of severe pulmonary arterial hypertension (combined treatment of chronic hypoxia and monocrotaline)
• Connexin 43 +/- transgenic mice
• TRPV4 -/- transgenic mice
• Newborn rats with pulmonary hypertension associated with bronchopulmonary dysplasia (15 days of hyperoxia)

Christelle Guibert

Pathophysiology of pulmonary and systemic circulation

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Roger Marthan
Bordeaux

Our team works on a real interface between cardio-vascular and pulmonary diseases and is composed of multidisciplinary researchers with various trainings (scientists, physicians, pharmacists). Our aims are to perform translational research with clinical trial when relevant.

Research Brief :

The main scientific scope of the team relates to biology of the pulmonary and systemic circulation. Regarding pulmonary circulation, we focus our research on (1) pulmonary hypertension (PH) (cellular and molecular mechanisms associated to vascular remodeling and reactivity as well as pharmacological treatments) and (2) impact of environmental factors (airborne pollution and hyperoxia). Regarding systemic circulation, our studies focus on actin cytoskeleton remodeling (i.e. podosomes in endothelial cells exposed to various factors such as VEGF and TGFbeta, key players of remodeling). By addressing vascular pathophysiology on pulmonary and systemic circulations, our team works on a real interface between cardio-vascular and pulmonary diseases. Our team is composed of multidisciplinary researchers with various trainings (scientists, physicians, pharmacists).

Specific objectives of the team are the following:
1. To address the role of Stretch-activated channels (SAC) and intercellular communications (connexins) in PH
2. To develop an animal model of bronchopulmonary dysplasia associated to PH in newborn and to address the role of SAC and intercellular communications in connection with theme 1
3. To address the impact of particulate pollution on the pulmonary circulation
4. To address systemic vascular remodeling (role of podosomes and connexin 40)

• **Methodologies Used :**

Biological material and main methodologies used:
(1) Freshly isolated vascular cells, cultured cells and tissu (pulmonary arteries) for molecular biology (PCR, qPCR), cellular biology (electron microscopy, Western Blot, siRNA, FACS, tests for migration, proliferation and apoptosis), immunohistochemistry, patch-clamp and fluorescent imaging (calcium, reactive oxygen species (ROS))
(2) Vessels (arterial rings, pressurized and cannulated small vessels) from animal models and human tissue (reactivity, electron paramagnetic resonance for measurement of ROS)
(3) Animal models of pulmonary hypertension and/or transgenic animals for in vivo and in vitro experiments
(4) Human tissue (pulmonary arteries and/or lung from adult and fetus)

Publications

Dumas de La Roque E, Bellance N, Rossignol R, Begueret H, Billaud M, dos Santos P, Ducret T, Marthan R, Dahan D, Ramos-Barbón D, Amor-Carro Ó, Savineau JP, Fayon M. (2012). Dehydroepiandrosterone reverses chronic hypoxia/reoxygenation-induced right ventricular dysfunction in rats., European Respiratory Journal. 40(6), 1420-1429

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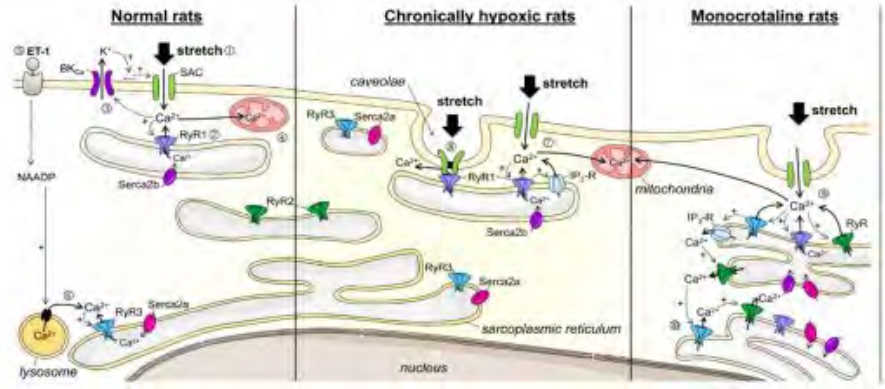
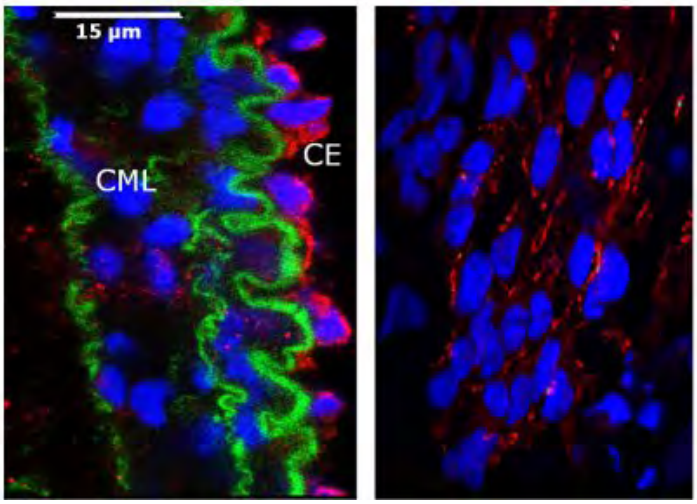
Summary of signaling pathways associated to stretch in pulmonary arterial smooth muscle cells.



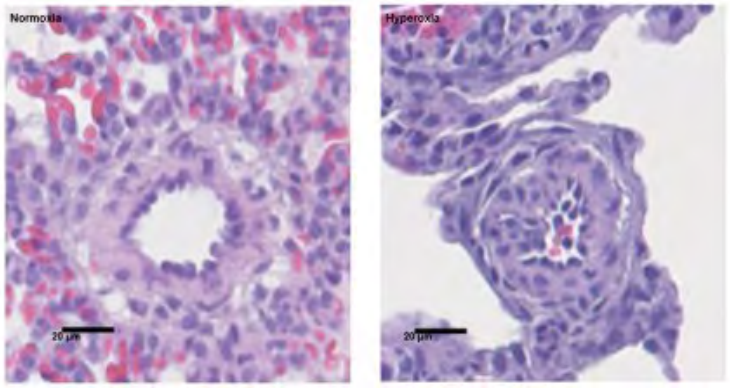
Signaling pathways in normal rats (left), rats suffering from chronically hypoxic pulmonary hypertension (middle) and rats suffering from pulmonary arterial hypertension induced by monocrotaline (right) (from Gilbert G. et al., Cardiovasc Res, 2014).

Connexin 43 immunofluorescent labeling (red).



Connexin 43 labeling is shown on a pulmonary arterial cross section (left) and on the endothelial side of an opened vessel (right). Nuclei are labelled in blue and autofluorescence of external and internal elastic lamina are in green. Labellings were observed with confocal microscope (Nikon TE2000). CML, smooth muscle cells, CE, endothelial cells.

Remodeling of intrapulmonary arteries (IPA) from newborn rats following 15 days of hyperoxia (90 %).



Left picture is an IPA from newborn rat breathing air (21 % O2) and right picture is an IPA from newborn rat breathing 90 % O2.

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GRED
GENETIQUE REPRODUCTION & DEVELOPPEMENT

Vincent Sapin

Translational approach to epithelial injury and repair

Université Clermont Auvergne
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Key facts

Team

• Researchers : 12
• Technicians : 0
• Postdoc fellows : 0
• PhD Students : 5

Translational approaches

• Patents : 0
• Clinical research grants : 0
• Industry partnerships : 0

International research links

• USA (Oregon, New-York, California)

Keywords

• Lung and fetal membranes
• ARDS
• PROM
• Pathophysiology
• RAGE
• Molecular biology
• Cellular Biology
• Animal models
• Clinical research

Biological Resources

• Cirspr CAS9 cells for RAGE and
NLRP
• Fetal membrane cohots and explants
• Mice model for ARDS
• RAGE -/- mice
• Primary and immortalized cells

Team working on epithelial injury and repair by using translational approaches.

Research Brief :

Following exo- and endogenous attacks, the attainment of the epithelial barrier integrity is an element found in human pathologies. The ability to repair such an epithelial attack conditions the evolution of these clinical events. Located at the intersections of many metabolic and inflammatory processes, the receptor for advanced glycation endproducts (RAGE) and its pathway could be of primary importance in this situation. The team has begun to demonstrate it on models of epithelial amniotic and pulmonary aggression encountered in 2 frequent pathologies (premature rupture of amniotic membranes (PROM) and acute respiratory distress syndrome (ARDS). Considering the complexity of the possible "RAGE ligand/isoform" combinations associated with the pathological activation of this pathway, it's essential to identify the importance of these different combinations and to determine if new ligands could be involved in PROM and ARDS. Using pharmacological and molecular approaches, we will identified abnormally modulated pathways that could be associated with the arising of both pathologies. Then, as the interaction of the epithelium with the cells of its near environment is a strong determinant of such aggression, the project aims to demonstrate the importance of RAGE pathway in cellular communications. Finally, availability of a mouse KO for RAGE will also allow us to study, in vivo, such impacts. Our results must permit to obtain diagnostic, prognostic and therapeutic advances.

• **Methodologies Used :**

- Cloning
- Cell tranfection
- Promotology studies and reporter gene
- Microscopy
- Western-blot
- qPCR
- Multiplex assay
- Elisa
- Crispr CAS9

Publications

M. Jabaudon, R. Blondonnet, L. Roszyk, B. Pereira, R. Guerin, S. Perbet, S. Cayot, D. Bouvier, L. Blanchon, V. Sapin and J. Constantin (2015). Soluble Forms and Ligands of the Receptor for Advanced Glycation End-Products in Patients with Acute Respiratory Distress Syndrome: An Observational Prospective Study, Plos one. 10(8), e0135857

D. Bouvier, M. Rouzaire, G. Marceau, C. Prat, B. Pereira, R. Lemarie, P. Deruelle, I. Fajardy, D. Gallot, L. Blanchon, A. Vambergue and V. Sapin (2015). Aquaporins and Fetal Membranes From Diabetic Parturient Women: Expression Abnormalities and Regulation by Insulin, J. Clin. Endocrinol. Metab. 100(10), 1270?9

M. Jabaudon, R. Blondonnet, L. Roszyk, D. Bouvier, J. Audard, G. Clairefond, M. Fournier, G. Marceau, P. Dechelotte, B. Pereira, V. Sapin and J. Constantin (2015). Soluble Receptor for Advanced Glycation End-Products Predicts Impaired Alveolar Fluid Clearance in Acute Respiratory Distress Syndrome., American journal of respiratory and critical care medicine. 192(2), 191?9

S. Mrozek, M. Jabaudon, S. Jaber, C. Paugam-Burtz, J. Lefrant, J. Rouby, K. Asehnoune, B. Allaouchiche, O. Baldesi, M. Leone, Q. Lu, J. Bazin, L. Roszyk, V. Sapin, E. Futier, B. Pereira and J. Constantin (2016). Elevated Plasma Levels of sRAGE Are Associated With Nonfocal CT-Based Lung Imaging in Patients With ARDS: A Prospective Multicenter Study, Chest. 150(5), 998?1007

A. Comptour, M. Rouzaire, C. Belville, N. Bonnin, E. Daniel, F. Chiambaretta, L. Blanchon and V. Sapin (2016). Lysyl oxidase-like 4 involvement in retinoic acid epithelial wound healing., Scientific reports. 6(), 32688

M. Rouzaire, A. Comptour, C. Belville, D. Bouvier, G. Clairefond, F. Ponelle, V. Sapin, D. Gallot and L. Blanchon (2016). All-trans retinoic acid promotes wound healing of primary amniocytes through the induction of LOXL4, a member of the lysyl oxidase family, The international journal of biochemistry & cell biology. 81(pt(A)), 10-19

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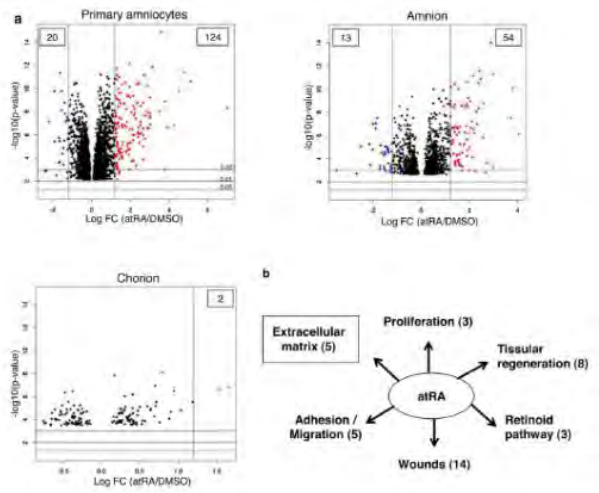
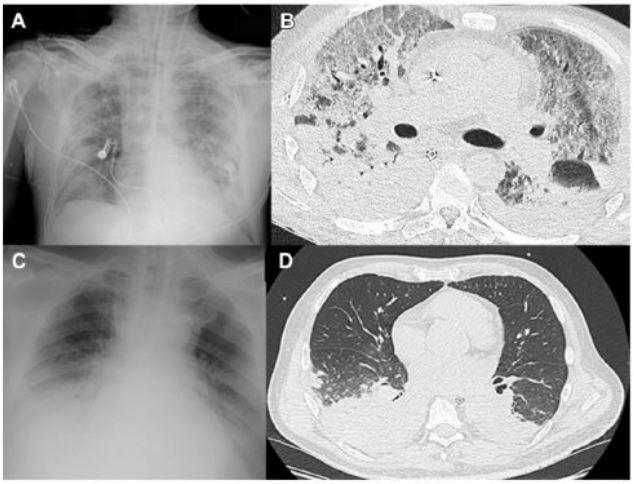
https://www.gred-clermont.fr/directory/team/fr/equipe-10-approche-translationnelle-des-lesions-epitheliales-et-de-leur-reparation/

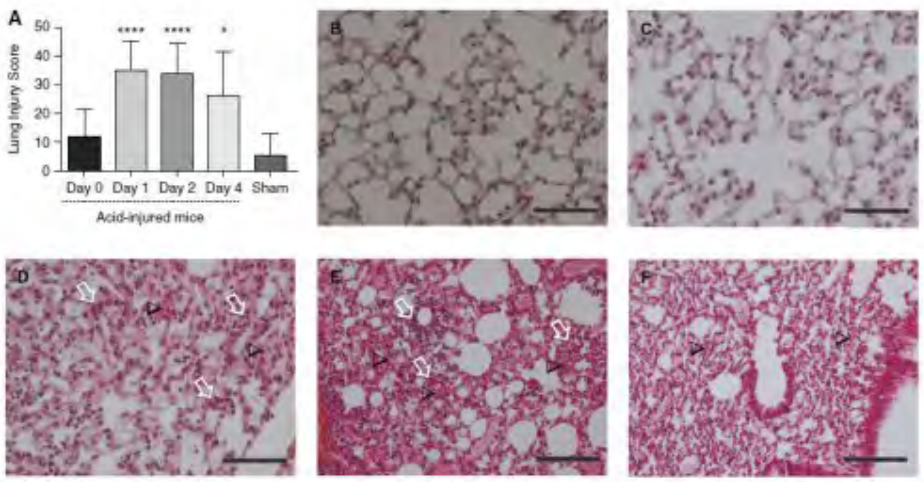
Transcriptomic analyses of atRA effects on human fetal membranes



Transcriptomic analysis was performed on amnion and chorion explants and primary amniocytes treated with atRA or its vehicle (DMSO) for 24 h (n=12). Volcano plots of the results obtained for each condition (a). Red and blue dots represent each probe up- or down-regulated after applying a restriction to the fold change (FC). Cellular pathways identified as most meaningful after Genomatix® analysis of atRA-regulated genes in amnion and primary amniocytes are shown in (b).

Bedside chest radio and CT scans of 2 characteristic patients with nonfocal (A, B), and focal (C, D)





(A) Lung injury scoring shows a significant injury on Days 1, 2, and 4 in injured animals as compared with sham control animals (n?=?6?8 for each time point). (B?F) Representative hematoxylin and eosin?stained sections at ×20 original magnification of sham and injured animals at all time points after acid aspiration. (B) Sham; (C) Day 0, injured; (D) Day 1, injured; (E) Day 2, injured; and (F) Day 4, injured.

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Dermatology

Guy Serre

Epithelial differentiation and rheumatoid autoimmunity

Université de Toulouse 3
(Université Paul Sabatier)
Inserm U1056
Guy Serre
Toulouse

Key facts

Team

- Researchers : 18
- Technicians : 14
- Postdoc fellows : 5
- PhD Students : 3

Translational approaches

- Patents : 3
- Clinical research grants : 1
- Industry partnerships : 5

International research links

- Belgium, Cameroon, Denmark, Greece, Germany, Israel, Sweden, The Netherlands, USA

Keywords

- dermatology
- Rheumatoid Arthritis
- autoimmunity
- ophtalmology
- genetics
- inflammation
- immunoassays
- enzymology
- sequencing
- cell biology

Biological Resources

- Biobanks of serum samples from patients with rheumatic diseases, some with clinical information
- Reconstructed human epidermis and knockout mouse models
- Library of DNA samples of patients with Keratoconus or ocular developmental defects

The description of autoantibodies to citrullinated proteins, of which we have identified the tissue targets and contributed to demonstrate the pathophysiological importance, has revolutionized the early diagnosis of Rheumatoid Arthritis and allowed the development of worldwide used diagnostic tests.

Research Brief :

Located within the biological research area of Toulouse Purpan Hospital, UDEAR laboratory is dedicated to the study of joint, skin and eye chronic diseases. Its goal is to highlight new diagnostic tools and therapeutic targets for these diseases, but also to understand at the fundamental level the physiological regulation of the corresponding organs. The laboratory is composed of 4 multidisciplinary groups. Two of them are dedicated to the study of terminal differentiation of the epidermis and its defects in skin diseases. More specifically, they investigate the molecular bases of epidermal barrier functions, and the pathophysiology and genetic basis of Ichthyoses and Atopic Dermatitis. A group improves the diagnosis and studies the pathophysiology of Rheumatoid Arthritis. It focuses on the involvement of the disease-specific anti-citrullinated protein autoantibodies, their role in macrophage activation and the characterization of their tissue targets. A fourth group, who joined UDEAR in January 2016, is interested in the terminal differentiation of the corneal and conjunctival epithelia, and in the genetics and pathophysiology of Keratoconus and diseases of ocular development.
The laboratory uses human sample collections, and is linked to 2 national hospital reference centers dedicated to rare genetic skin diseases and to Keratoconus, respectively. It is relied on a large network of academic and industrial collaborations, at a local, national and international level.

- **Methodologies Used :**

Cytology, immunohistology, solid phase immune complex reconstitution, cell sorting, cell culture, flow cytometry, protein separation (chromatography, electrophoresis), protein analysis (Western blot, ELISA), RNA interference, confocal microscopy, electron microscopy, new generation sequencing, quantitative RT-PCR, transcriptomics, proteomics, genome wide association study, exome sequencing, recombinant protein production, knockout mouse models.

Publications

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Cornillet M, Sebbag M, Verrouil E, Magyar A, Babos F, Ruyssen-Witrand A, Hudecz F, Cantagrel A, Serre G, Nogueira L (2014). The fibrin-derived citrullinated peptide beta60-74Cit60,72,74 bears the major ACPA epitope recognised by the Rheumatoid Arthritis-specific anti-citrullinated fibrinogen autoantibodies and anti-CCP2 antibodies, Ann Rheum Dis. 73(6), 1246-1252

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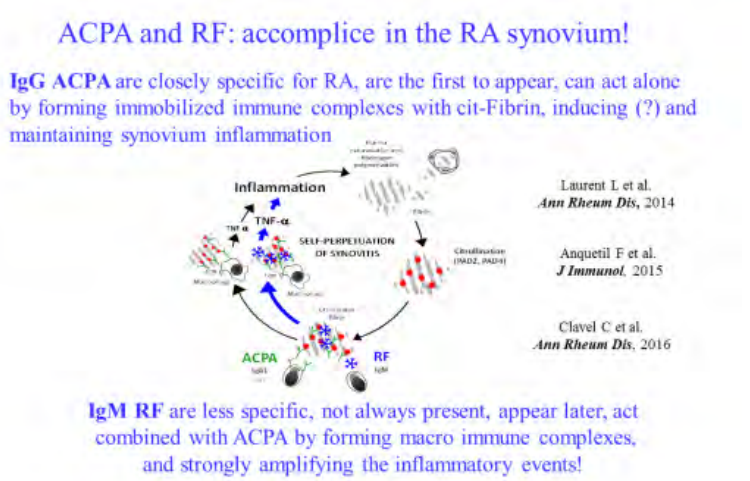
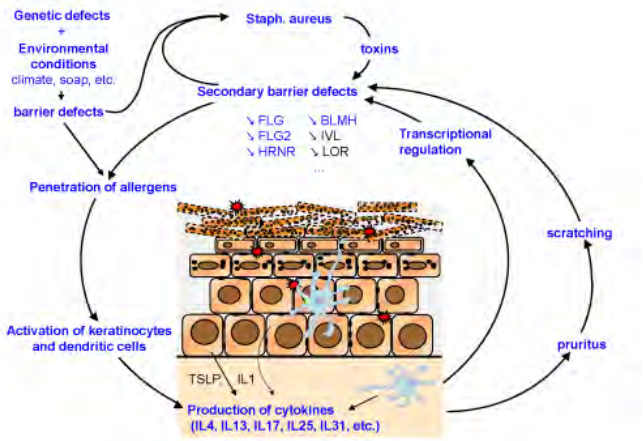
Involvement of autoantibodies to citrullinated proteins (ACPA) and RF in Rheumatoid Arthritis



Atopic Dermatitis: a new pathophysiological model



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Key facts

Team

- Researchers : 3
- Technicians : 1
- Postdoc fellows : 1
- PhD Students : 2

Translational approaches

- Patents : 2
- Clinical research grants : 0
- Industry partnerships : 0

Keywords

- lymphocytes
- vitiligo
- pigmentation
- dermatology
- Immunology
- Primary culture of melanocytes and keratinocytes
- 3D reconstructed epidermis with melanocytes
- Immunofluorescence
- Flow cytometry
- RT-PCR, ELISA

Biological Resources

- In vitro model of reconstructed human pigmented epidermis and In vitro model of depigmentation
- Blood from healthy volunteer donors (Etablissement Français du Sang) - Healthy skin samples are obtained from Bordeaux Hospital as discarded skin from plastic surgery
- Blood samples and skin biopsies are obtained from patients with skin inflammatory disorders seen in the Dermatology department of Bordeaux Hospital (A. Taieb, J. Seneschal) - Healthy

Julien Seneschal
Katia Boniface

Immuno-dermatology ATIP-AVENIR

Université de Bordeaux
Inserm 1035
Alain Taieb
Bordeaux

Our team has a leading position in translational research from bench to bedsides and our research is focused on the interplay between the skin immune system and epidermal cells in human, allowing a better understanding of inflammatory skin disorders and skin lesions associated with systemic diseases

Research Brief :

The team is focusing its research on the immune mechanism involved in skin inflammatory diseases, in particular Vitiligo, the most common skin depigmenting disorder. Based on a strong clinical research program dedicated to this pathology in the Dermatology department (Bordeaux Hospital), National Reference Center for Rare Skin Diseases, and the support of the "Vitiligo European Task Force" international group, we have developed basic and translational human research studies exploring both the innate and the adaptive immune responses in vitiligo. This approach has led to the identification of the role of the Type I Interferon signature in disease initiation and the involvement of memory T cells expressing CXCR3. Our main goal is to better understand the link between immunity and melanocyte loss in vitiligo to identify new therapeutic targets. We explore the role of inflammatory cytokines on the function, survival and adhesion of melanocytes, the cell responsible for pigmentation. Part of our research is also focused on depigmentation occurring as a side effect in patients receiving immunotherapies. Moreover, our research is translated to pigmentation disorders affecting inflammatory skin diseases, such as psoriasis or scleroderma.
Our team is part of the "Fédération Hospitalo-Universitaire" ACRONIM, Bordeaux University, and works in collaboration with the Immunology unit (CNRS, UMR 5164) on the pathogenesis of systemic diseases.

- **Methodologies Used :**

1 - Isolation and expansion of blood and skin immune cells for: Phenotyping: multiparametric analyses by flow cytometry, immunohistochemistry,immunofluorescence studies / Functional assays: cell proliferation and survival (CFSE, MTT), apoptosis (annexin V, caspase 3, tunel assay)
2 - Impact of soluble inflammatory factors on epidermal cell cultures: Primary cultures of melanocytes and keratinocytes; in vitro 3D reconstructed pigmented epidermis / Immunohistochemistry, Immunofluorescence studies / ELISA, multiplex ELISA / Real-time RT-PCR analysis
3 - Identification of biomarkers in serum and skin samples of patients: ELISA, multiplex ELISA/ Real-time RT-PCR analysis

Publications

Boniface K, Bak-Jensen KS, Li Y, Blumenschein WM, McGeachy MJ, McClanahan TK, McKenzie BS, Kastelein RA, Cua DJ, de Waal Malefyt R (2009). Prostaglandin E2 regulates Th17 cell differentiation and function through cyclic-AMP and EP2/EP4 receptor signaling, J Exp Med. 206(3), 535-48

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J.Seneschal, R.A.Clark, A. Gehad, Clare M. Baecher-Allan, T.S. Kupper. (2012). Human Epidermal Langerhans Cells Maintain Immune Homeostasis in Skin by Activating Skin Resident Regulatory T Cells, Immunity. 36(5), 873-84

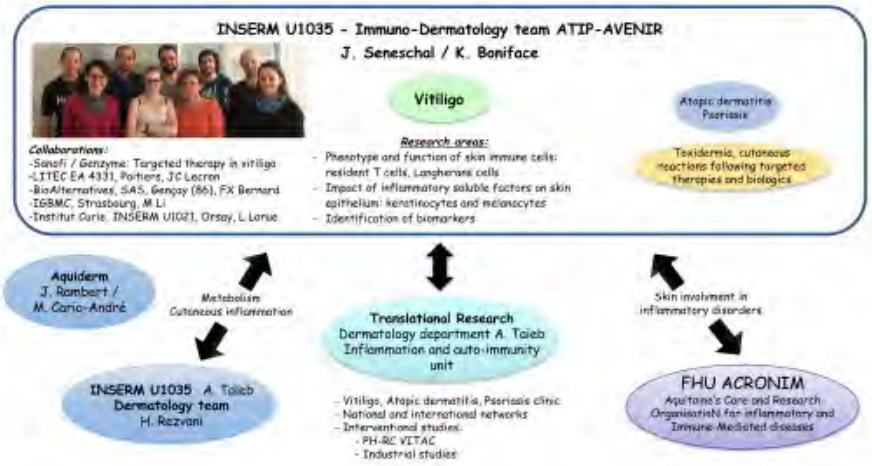
A.Bertolotti, K.Boniface, B.Vergier, M.D.Mossalayi, A.Taieb, K.Ezzedine, J.Seneschal (2014). Type I Interferon signature in the initiation of the immune response in vitiligo. Pigment Cell Melanom Res., Pigment Cell Melanoma Res. 27(3), 39-4078-

C. Jacquemin, N. Schmitt*, C. Contin-Bordes*, Y. Liu, P. Narayanan, J. Seneschal, T. Maurouard, D. Dougall, E. Spence Davizon, H. Dumortier, I. Douchet, L. Raffray, C. Richez, E. Lazaro, P. Duffau, M.E. Truchetet, L. Khoryati, P. Mercié, L. Couzi, P. Merville, T. Schaeverbeke, J.F. Viallard, J.L. Pellegrin, J.F. Moreau, S. Muller, R.L. Coffman, V. Pascual, H. Ueno* and P. Blanco*. (equally contribution) (2015). OX40 Ligand Contributes to the Pathogenesis of Autoiimunity by Promoting T follicular Helper Response., Immunity. 42(6), 1159-70*

M. Larsabal, A. Marti, C. Jacquemin, J. Rambert, D. Thiolat, L. Dousset, A. Taieb, C. Dutriaux, S. Prey, K. Boniface, J. Seneschal* (equally contribution) (2017). Vitiligo-like lesions occurring in patients receiving anti-programmed cell death-1 therapies are clinically and biologically distinct from vitiligo, J Am Acad Dermatol.. (),*

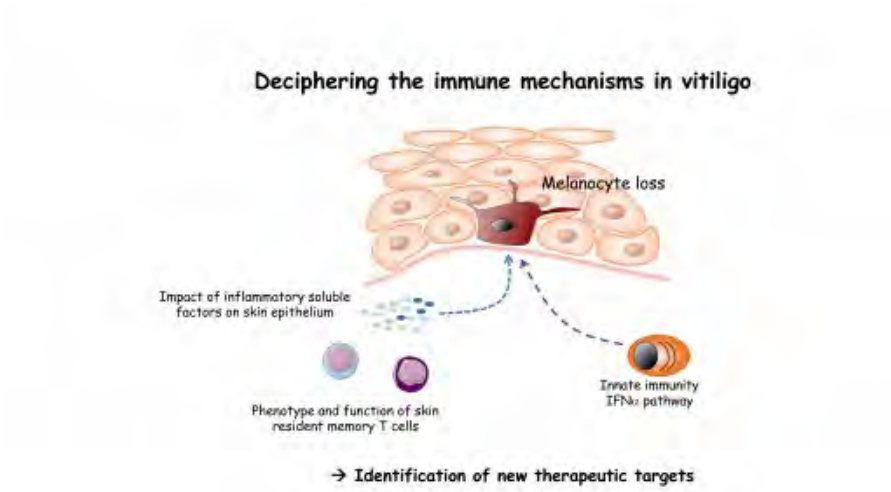
Seneschal Julien - julien.seneschal@chu-bordeaux. fr - 0557571094 - http://u1035-inserm.fr/fr/institution

Immunology-dermatology team ATIP-AVENIR



Our Immuno-dermatology team is focusing its research on human depigmenting skin inflammatory disorders, in particular vitilio. Our main goal is to understand the role of the skin immune sytem in this disease to identify new therapeutic targets. We are also extending our research to depigmentation associated with other skin or systemic inflammatory diseases. Our work is done is close collaboration with the dermatology department of Bordeaux Hospital. National collaborations have been developed

Immunology-dermatology project overview



To understand the interplay between the skin immmune system and epidermal cells that lead to melanocyte loss,in vitro and ex vivo studies are performed on human tissues to characterize:
- the phenotype and function of skin immune cells (T cells, dendritic cells)
- the impact of inflammatory soluble factors on skin epithelium: keratinocytes and melanocytes

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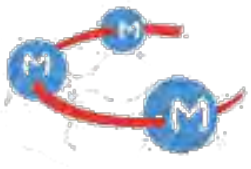
Diabetes



Mireille Cormont Jean-François Tanti

Cellular and Molecular Physiopathology of Obesity and Diabetes

Université de Nice
Sophia-Antipolis
Inserm U1065
Patrick Auberger
NICE

Our team performs studies from molecular to cells and animal level in order to have an integrative view of the dysfunction of adipose tissue and metabolism linked to obesity and diabetes

Key facts

Team

- Researchers : 6
- Technicians : 1
- Postdoc fellows : 1
- PhD Students : 2

Translational approaches

- Patents : 1
- Clinical research grants : 0
- Industry partnerships : 1

International research links

- Spain
- Czech Republic

Keywords

- obesity
- diabetes
- insulin resistance
- adipose tissue
- signaling
- glucose transport
- trafficking
- Inflammation
- Western blot
- in vitro ubiquitin assay
- glucose and lipid metabolism in cells and organs
- primary adipocyte culture
- adipocyte transfection
- yeast two-hybrid screening
- real-time PCR
- cell imaging
- animal metabolism

Biological Resources

- antibodies
- model of obese mice
- primary adipocytes
- primary macrophages

Research Brief :

The research of our team deals with the pathophysiology of the insulin resistance in obesity and type 2 diabetes (T2D), focusing on the mechanisms involved in adipose tissue (AT) dysfunction in obesity and how this dysfunction is linked with the development of insulin resistance. Our goal is to decipher how stresses and stress responsive pathways that develop in AT during obesity (inflammation, hypoxia, DNA damage) alter its metabolic and endocrine function and to determine if and how these pathways can alter liver functions.
We develop research activities along two related and highly integrated areas:
1) To unravel and characterize novel molecular mechanisms and signaling pathways induced by AT stresses causing metabolic dysfunction of AT and adipocyte insulin resistance.
2) To identify new genetic and epigenetic players controlling liver metabolism and to decipher their implication in insulin resistance. This axis was initiated by Jean-François Louet (CR1 CNRS) who joined the team by the end of 2013 (see below: organization of the team). JF Louet has a solid background in the study of the transcriptional control of liver metabolism by multi-proteins co-regulator complexes, especially the steroid receptor coactivator (SRC) family.
We combine molecular and mechanistic studies using different cell models, studies in preclinical animal models and translational research to evaluate the clinical relevance of the animal and in vitro findings.

- **Methodologies Used :**

Primary human adipocytes in culture
Cell signaling and gene expression quantification
Metabolic studies in isolated adipocytes and muscles and in animals
Cellular imaging of protein trafficking
Animal models of obesity and diabetes (KO mice, High-Fat diet and genetically obese mice)

Publications

Jager J, Gremeaux T, Gonzalez T, Bonnafous S, Debard C, Laville M, Vidal H, Tran A, Gual P, Le Marchand-Brustel Y, Cormont M, Tanti JF (2010). Tpl2 Kinase Is Upregulated in Adipose Tissue in Obesity and May Mediate Interleukin-1 beta and Tumor Necrosis Factor-alpha Effects on Extracellular Signal-Regulated Kinase Activation and Lipolysis, DIABETES. 59(1), 61-70

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Key facts

Team

- Researchers : 3
- Technicians : 2
- Postdoc fellows : 4
- PhD Students : 4

Translational approaches

- Patents : 3
- Clinical research grants : 1
- Industry partnerships : 3

International research links

- Germany, Austria, Spain,
- Belgium, Sweden, Denmark
- USA, Canada,UK,

Keywords

- Reprogramming
- GABA
- Diabetes
- Pax4
- Arx
- Mouse
- Molecular Biology

Patrick Collombat

Diabetes Genetics

Université de Nice
Sophia-Antipolis
Inserm U1091
Stéphane Noselli
Nice

We use reprogramming to convert pancreatic cells into insulin-producing beta-cells

Research Brief :

Our group is involved diabetes research. Both Type I Diabetes (insulinodependent) and Type II (non insulinodependent) diabetes ultimately result in the selective loss of insulin-producing beta-cells in the endocrine pancreas. The subsequent lack in insulin hormone induces a blood hyperglycemia that may be attenuated by daily injection of exogenous insulin hormone. Nevertheless, due to variations in glycemia, vascular damages, blindness, amputation or even death may occur.
We belong to a JDRF-funded consortium whose goal is to gain further insight into the mechanisms regulating the genesis of the mouse pancreas and apply this knowledge to improve the treatment of diabetes. Toward this aim, using the mouse as a model, we have identified two transcription factors, Arx and Pax4, playing a crucial role in the genesis of the different endocrine cell subtypes, including insulin-secreting beta-cells. Importantly, we showed that the forced expression of Pax4 in alpha-cells is sufficient to induce their continuous regeneration and conversion into cells displaying a beta-cell phenotype.
Aiming to eventually apply these finding to human, we searched for compounds able to induce similar processes. GABA was thus identified and found that it was able to induce alpha-cell-mediated beta-like cell neogenesis in the mouse. The beta-like cells thereby generated were functional and could reverse several times the consequences of chemically-induced diabetes in vivo.

Methodologies Used :

- Mouse
- Immunohistochemistry
- Molecular Biology
- qPCR

Publications

Collombat P, Xu X, Ravassard P, Sosa-Pineda B, Dussaud S, Billestrup N, Madsen OD, Serup P, Heimberg H, Mansouri A (2009). The ectopic expression of Pax4 in the mouse pancreas converts progenitor cells into alpha and subsequently beta cells., Cell. 138(3), 449-62

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GABA induces beta-like cell regeneration in mice rendered diabetics

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Key facts

Team

- Researchers : 4
- Technicians : 5
- Postdoc fellows : 2
- PhD Students : 3

Translational approaches

- Patents : 4
- Clinical research grants : 3
- Industry partnerships : 5

International research links

- Belgium, Italy, Germany, Switzerland, Sweden, UK
- Australia, USA

Keywords

- Diabetes
- Obesity
- MAIT-NKT cell
- Treg cell
- Epitopes
- Pancreatic islet
- Humanized mice
- Immunoregulation

Biological Resources

- Cohorts of diabetes patients
- Transgenic mice
- PBMC of diabetic patients

Agnès Lehuen

Immunology of diabetes

Université Paris Descartes
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Role of innate and adaptative immune cells in diabetes

Research Brief :

Type 1 diabetes (T1D) is an early onset autoimmune disease caused by the destruction of beta pancreatic cells by the immune system, whereas type 2 diabetes (T2D) is associated to low grade inflammation that contributes to the induction of insulin resistance. The objective of our projects is to decipher the role of specific innate and adaptive immune cells and their molecular pathways in the development of diabetes to develop therapies based on immune-regulation and antigen-specific strategies to induce tolerance toward ?-pancreatic cells. These studies are based on newly developed mouse models and the use of patient samples, mainly from our close relationship with the clinical Diabetology Department of the Cochin Hospital as well as from other endocrinology and nutrition clinical departments.
We are analyzing the role of innate-like T cells, NKT and Mucosal Associated Invariant (MAI)T cells recognizing bacterial ligands, in the physiopathology of both T1D and metabolic diseases.
We are determining self-epitopes recognized by pathogenic and regulatory T cells in patients and in humanized mouse models of T1D.
Genetic factors are involved in both types of diabetes, particularly those related to the control of day-night rhythm. Our previous work identified the circadian-rhythm related gene Bmal2 (Arntl2) as an interesting candidate in diabetes physiopathology.
All these approaches will allow the development of new biomarkers and innovative therapeutic strategies against diabetes

- **Methodologies Used :**

Mouse models of type 1 diabetes and obesity
Humanized mouse model of type 1 diabetes
Viral infections of mouse model of type 1 diabetes
MAIT cell analysis in type 1 diabetes and obesity (human and mouse)
ELISPOT assay to detect autoreactive T cells (human and mouse)

Publications

Diana J., Y. Simoni, L. Furio, L. Beaudoin, B. Agerberth, F. Barrat, and A. Lehuen (2013). Crosstalk between neutrophils, B-1a cells and plasmacytoid dendritic cells initiates autoimmune diabetes, Nature Medecine. 19(), 65-73

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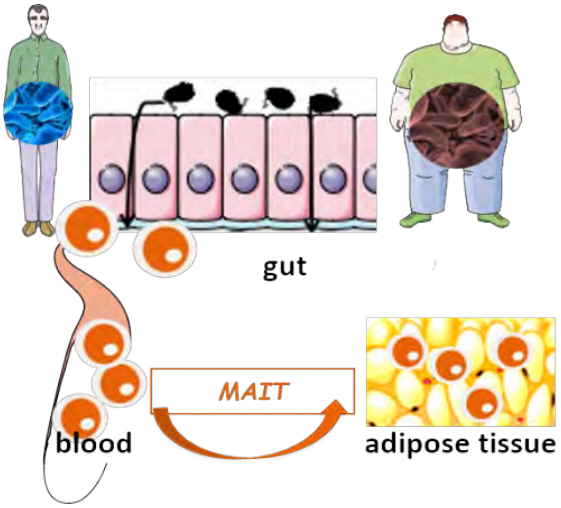
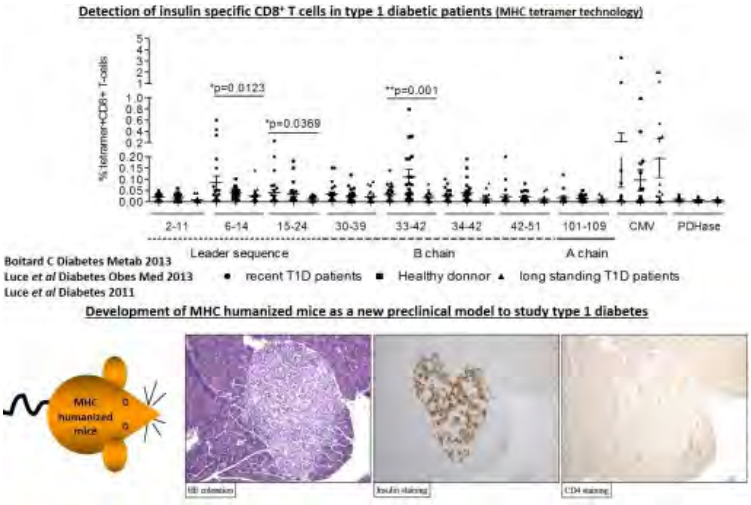


Characterisation of autoreactive T cells in mouse models and patients



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Roberto Mallone

DeARLab - Diabetes & Autoimmunity Research Laboratory

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Paris

Innovative technologies are developed to move towards 'immune staging' strategies that may offer novel diagnostic and therapeutic options for autoimmune diseases.

Key facts

Team

- Researchers : 3
- Technicians : 4
- Postdoc fellows : 3
- PhD Students : 2

Translational approaches

- Patents : 5
- Clinical research grants : 2
- Industry partnerships : 4

International research links

- Belgium
- Denmark
- Germany

Keywords

- type 1 diabetes
- T cell
- beta cell
- antigen
- tolerance
- HLA tetramer
- ELISpot
- T-cell cloning
- TCR sequencing
- Cytotoxicity

Biological Resources

- TRAKR cohort & biobank
- INNODIA cohort & biobank
- Autoimmune T-cell clones
- ImMaDiab cohort & biobank

Research Brief :

Type 1 diabetes (T1D) prevalence is steadily increasing in industrialized countries, with an incidence of 15 new diagnoses/100,000 inhabitants/year in France, which further increases of 3-4% every year. As it mainly affects children and young adults leading to lifelong treatments and frequent long-term complications (cardiovascular diseases, end-stage renal failure, blindness), it is a highly debilitating disease and an important voice of public health expense.

Type 1 diabetes (T1D) is an autoimmune disease caused by autoreactive T lymphocytes which destroy insulin-producing pancreatic islet beta-cells. Despite this knowledge, neither the diagnosis nor the therapy of T1D targets pathogenic T lymphocytes. Our research projects therefore aim at exploiting these T lymphocytes as disease biomarkers and as therapeutic targets to prevent beta-cell destruction, and at understanding the cross-talk between T lymphocytes and pancreatic beta cells.

The long-term objective is to develop an immune "staging" and intervention protocol in subjects at risk for T1D development, in order to detect and block beta-cell autoimmunity at an early stage. The strategies developed may lead to a paradigm shift in the approach to T1D by identifying and treating the immune disease early, before the appearance of its metabolic consequences. By targeting the mechanisms underlying disease development, such strategies would pave the way to T1D prevention and treatment.

- **Methodologies Used :**

* Human and mouse models
* Cell culturing and T-cell cloning
* Flow cytometry and HLA tetramers
* ELISpot

Publications

Martinuzzi E, Afonso G, Gagnerault MC, Naselli G, Mittag D, Combadière B, Boitard C, Chaput N, Zitvogel L, Harrison LC, Mallone R (2011). acDCs enhance human antigen-specific T-cell responses., Blood. 118(8), 2128-37

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Key facts

Team

- Researchers : 4
- Technicians : 3
- Postdoc fellows : 5
- PhD Students : 2

Translational approaches

- Patents : 3
- Clinical research grants : 3
- Industry partnerships : 8

Keywords

- Pancreas
- development
- in vitro bioassays
- in vivo bioassays

Biological Resources

- Human beta cell lines
- Rodent bioassay for cell differentiation

Raphaël Scharfmann

Control of pancreatic endocrine cell development

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We have gained expertise in developing assays in reconstituted rodent and human models to define intercellular signals regulating pancreatic beta cell development.

Research Brief :

Type-1 diabetes is caused by an autoimmune destruction of insulin producing beta cells resulting in insulin deficiency. Insulin therapy is unsatisfactory. Thus defining new strategies (cell or regenerative therapies) as basis to cure diabetic patients represents a major challenge. Beta cells develop from pancreatic progenitors that proliferate and next differentiate into functional insulin-producing cells. This is a complex process, each step being controlled by specific signals. Theoretically, beta cell mass can be enhanced by: i) activating the proliferation of pancreatic progenitors; ii) activating their differentiation into beta cells; iii) activating the proliferation of beta cells themselves. During the past years, we developed tools based on rodent models to search for signals controlling each step of beta cell development. We developed strategies to transfer to reconstituted human models, data generated in rodent models. We also developed the first available human beta cell lines (a premiere). We generated new results and hypotheses concerning signals controlling each step of pancreatic development. We also dissected specific forms of neonatal diabetes in Human, which permits to define new treatments for children with neonatal diabetes. We are currently continuing this work which is important on a cognitive point of view, but also to define new approaches to find a cure for diabetes.

- **Methodologies Used :**

Bioassays to define signals regulating beta cell development.
In vitro and in vivo bioassays.
Reconstituted rodent and human bioassays.
Methodologies to develop human beta cell lines.

Publications

Ravassard P, Hazhouz Y, Pechberty S, Bricout-Neveu E, Armanet M, Czernichow P, Scharfmann R. (2011). A genetically engineered human pancreatic ? cell line exhibiting glucose-inducible insulin secretion., J Clin Invest. (),

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Eric Renard

Determinants and correction of insulin secretion loss in diabetes

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Jean-Philippe Pin
MONTPELLIER

Our team was the first one that historically implanted an artificial beta cell in diabetic humans in 2000 and tested artificial pancreas in ambulatory conditions in diabetic patients in 2011.

Key facts

Team

- Researchers : 5
- Technicians : 1
- Postdoc fellows : 1
- PhD Students : 0

Translational approaches

- Patents : 1
- Clinical research grants : 6
- Industry partnerships : 5

International research links

- Netherlands
- Italy
- USA

Keywords

- islet transplantation
- Diabetes
- insulin
- artificial pancreas
- severe obesity
- insulin delivery devices
- continuous glucose monitoring
- closed-loop algorithms
- bariatric surgery
- islet isolation

Biological Resources

- plasma samples, islet cells

Research Brief :

Our research program is based on developing artificial pancreas as a therapy of diabetes and on deciphering the factors determining the occurrence of diabetes in severe obesity. It also includes research on the development of islet transplantation and bio-artificial pancreas.

- **Methodologies Used :**

Pumps for continuous insulin delivery
Continuous glucose monitoring
Closed-loop algorithms
Bariatric surgery
Islet transplantation

Publications

Spaan NA, Teplova AE, Renard E, Spaan JAE (2014). Implantable insulin pumps: an effective option with restricted dissemination., Lancet Diabetes Endocrinol. 2(5), 358-60

Kovatchev BP, Renard E, Cobelli C, Zisser HC, Keith-Hynes P, Anderson SM, Brown SA, Chernavvsky DR, Breton MD, Mize LB, Farret A, Place J, Bruttomesso D, Del Favero S, Boscari F, Galasso S, Avogaro A, Magni L, Di Palma F, Toffanin C, Messori M, Dassau E, Doyle FJ III. (2014). Safety of outpatient closed-loop control: first randomized crossover trials of a wearable artificial pancreas., Diabetes care. 37(7), 1789-96

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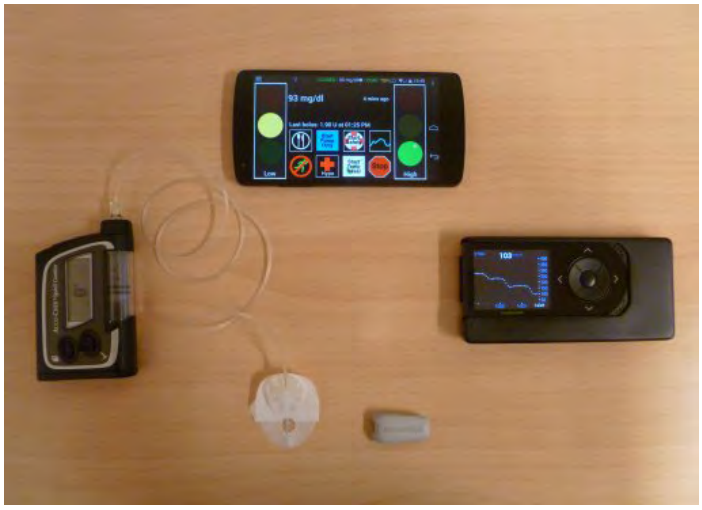
Components of a wearable model of artificial pancreas



Outpatient trial of artificial pancreas in children

Components of an artificial pancreas for outpatient trial in children

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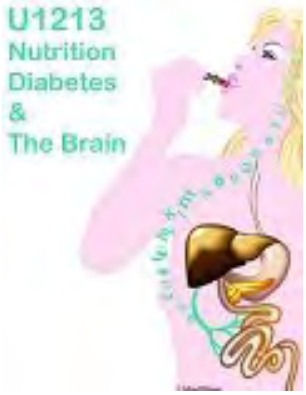

Gilles Mithieux

Nutrition, Diabetes and the Brain

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> ***We uncovered glucose production by the intestine and its paradoxical benefits on energy (food intake, energy expenditure) and glucose (insulin sensitivity, insulin secretion) homeostasis, which is a basis of our research project.***

Key facts

Team

- Researchers : 4
- Technicians : 5
- Postdoc fellows : 2
- PhD Students : 3

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 5

International research links

- Portugal
- USA
- Sweden

Keywords

- Endogenous glucose production
- insulin sensitivity
- diabetes
- obesity
- liver
- kidney
- intestine
- glucose-6 phosphatase
- microsurgery
- determination of glucose fluxes
- transgenesis

Biological Resources

- cell lines
- transgenic mice

Research Brief :

The project deals with the respective roles of the glucose-producing organs (the liver, kidney and small intestine) in the mechanisms of control of glucose and energy homeostasis. We have recently shown that endogenous glucose production (EGP) by the small intestine exerts, paradoxically, a beneficial role in this homeostasis. It activates a nervous signal, starting from the walls of the portal vein (the so-called portal glucose signal), which initiates centrally a satiety phenomenon, and at the hepatic level, a potentiation of the suppression of glucose production and an increase in insulin sensitivity. This paradigm has allowed us to explain by protein-enriched diets and the rapid amelioration of obesity and diabetes by dietary proteins or fibers and after gastric bypass surgery.
This led us to propose a novel concept of the role of EGP in the control of glucose and energy homeostasis: EGP by the liver should be deleterious, initiating insulin-resistance and further frank diabetes, whereas EGP by the small intestine would be beneficial in energy homeostasis.
To further document this novel concept in the field of obesity and diabetes, we created novel mice models of time-dependent and organ-specific deletion (or overexpression) of glucose-6 phosphatase (the key enzyme of EGP). These models allow us to contrast diabetes with the mirror disease (the Human glucose-6 phosphatase deficiency), for a better understanding of both the epidemic and the rare diseases.

• Methodologies Used :

Microsurgery in rats and mice
Energy (food intake, energy metabolism) and glucose (glucose tolerance, insulin sensitivity) homeostasis in rodents
Time-dependent and tissue-specific deletion (or overexpression) of glucose production in mice
Use of glucose-labeled tracers to quantify whole body and organ-specific glucose fluxes
Behavioral studies in relation with food intake and anxiety-depression

Publications

MUTEL E, ABDUL-WAHED A, RAMAMONJISOA N, STEFANUTTI A, HOUBERDON I, PILLEUL F, BEUF O, PENHOAT A, MITHIEUX G & RAJAS F (2011). Targeted deletion of liver glucose-6 phosphatase mimics glycogen storage disease type 1a including the development of multiple adenomas, Journal of Hepatology. 54(), 529-537

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DE VADDER F, KOVATCHEVA-DATCHARY P, GONCALVES D, VINERA J, ZITOUN C, DUCHAMPT A, BACKHED F & MITHIEUX G (2014). Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits, Cell. 156(), 84-96

ABDUL-WAHED A, GAUTIER-STEIN A, CASTERAS S, SOTY M, ROUSSEL D, ROMESTAING C, GUILLOU H, TOURETTE JA, PLECHE N, ZITOUN C, GRI B, SARDELLA A, RAJAS F & MITHIEUX G (2014). A link between hepatic glucose production and peripheral energy metabolism via hepatokines, Molecular Metabolism. 3(), 531-543

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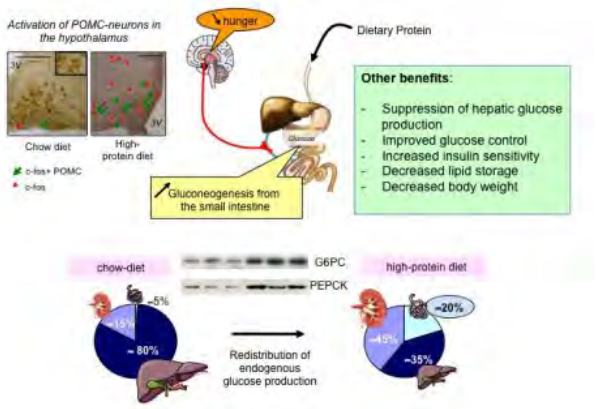
Gut-brain glucose signaling by intestinal gluconeogenesis and associated benefits



describes the gut-brain neural circuit initiated by intestinal gluconeogenesis, from the induction of gluconeogenesis genes up to the central and peripheral benefits in glucose and energy homeostasis. The situation of protein-feeding is illustrated. Comparable chain of processes take place under the action of dietary fibers or after gastric bypass surgery.

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Jennifer Rieusset

Organelle communication and diabetes

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Key facts

Team

• Researchers : 6
• Technicians : 3
• Postdoc fellows : 0
• PhD Students : 2

Translational approaches

• Patents : 2
• Clinical research grants : 6
• Industry partnerships : 2

Keywords

• Type 2 diabetes
• insulin resistance
• skeletal muscle
• endoplasmic reticulum
• mitochondria
• Organelle communication
• pancreas
• calcium signaling
• insulin signaling and secretion
• liver
• mice models of type 2 diabetes
• clinical intervention
• Primary cells in culture
• cellular signaling
• Membrane contact site
• Insulin sensitivity
• glucose-induced insulin secretion
• oxidatives capacities
• Mitochondria dynamics and function
• ER stress
• Subcellular fractionation
• In situ PLA
• Electronic microscopy

Biological Resources

• human myotubes in primary culture,
• human beta islets,
• tissues from high-fat and high-sucrose diet-fed mice and ob/ob mice
• Mitochondria-associated ER membranes (MAM) from midce models of T2D

Our major strengh is to have a double expertise in both skeletal muscle insulin sensitivity and beta cell function, in order to identify common mechanisms to their metabolic alterations and to propose new and more effective preventive and/or therapeutic targets against type 2 diabetes.

Research Brief :

Our team, managed by Charles Thivolet and myself, focuses on molecular mechanisms of altered insulin action and secretion in type 2 diabetes (T2DM). Among these mechanisms, we focus on the role of two key intracellular organelles: mitochondria and endoplasmic reticulum (ER). Both organelles interact at contact points, called MAM (mitochondria-associated endoplasmic reticulum membranes), in order to exchange both lipids and calcium, 2 metabolites that play a key role in metabolic homeostasis. We recently identified a new role of MAM in the control of insulin action and secretion, as well as organelle miscommunication in liver, skeletal muscle and beta cells of obese and diabetic mice.
The general goal of our research program is to better characterize the nature and the physiological significance of MAM in the control of glucose homeostasis and their roles in the pathogenesis of T2DM. More specifically, our specific aims are:
1) To identify the molecular nature of MAM actors and their functional roles,
2) To characterize the physiological significance of MAM in the control of insulin action and secretion,
3) To identify the regulators of MAM and their functional impacts,
4) To validate if the MAM could be a new target for the treatment of T2DM.
Ultimately, our scientific project will clarify the mechanisms by which MAM are involved in the pathogenesis of T2DM and should determine if MAM could be a new target to improve both insulin action and secretion in T2DM.

• **Methodologies Used :**

- Primary cultures of human myotubes, hepatocytes and beta cells of pancreas
- Adenoviral overexpression or invalidation by RNAi of genes in vitro
- Analysis of the structure, density and the functions of mitochondria (electronic microscopy, respiration, ATP synthesis, fatty acids oxidation)
- Analysis of the homeostasis of endoplasmic reticulum (electronic microscopy, real-time PCR, Western blotting)
- Analysis of ER-mitochondria interactions (electronic microscopy, in situ PLA, subcellular fractionation)
- Analysis of insulin signalling (immuno-precipitation, western-blotting)
- Analysis of the mass and functions of beta cells

Publications

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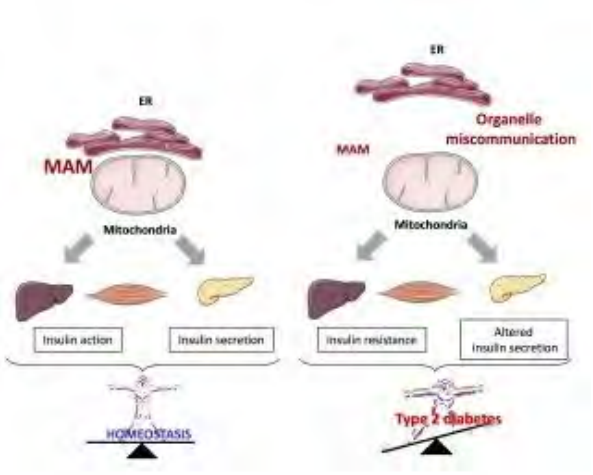
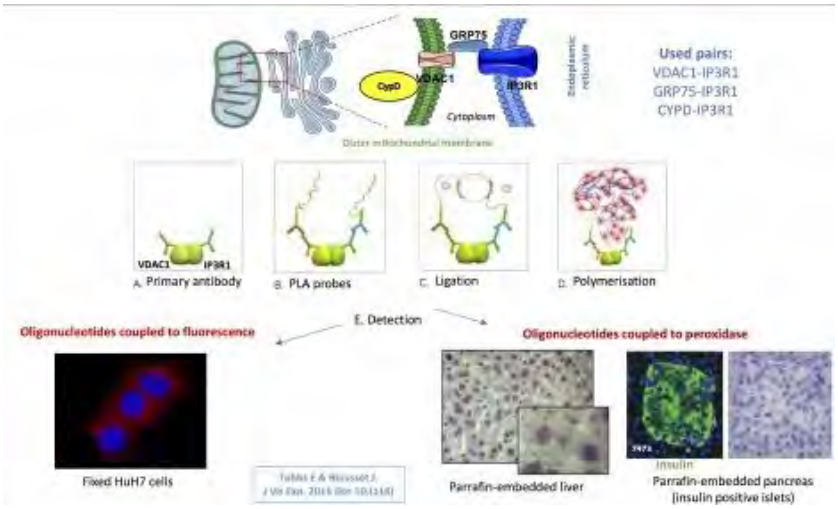
Scientific objectives of our team



The general goal of our research is to better understand the role of ER-mitochondria interactions (known as MAM for mitochondrial-associated membranes) in the control of glucose homeostasis (in insulin action and secretion) and in the pathogenesis of type 2 diabetes.

Visualization and quantification of ER-mitochondria interactions by in situ Proximity Ligation Assay



Schematic representation of the VDAC1/GRP75/IP3R1 complex at MAM interface and of in situ PLA steps for visualization of VDAC1/IP3R1, GRP75/IP3R1 or CypD/IP3R1 interactions.

A) incubation of cells or tissues with two different primary antibodies, one directed against the IP3R1 channel in the ER, and another one against a mitochondrial protein (VDAC or CypD) or the chaperone Grp75, B-C) circularization and ligation of connector oligonucleotides of secondary antibodies when proteins are less than 40 nm away, D) rolling circle amplification with polymerase and E) detection of the product with fluorescent or peroxidase-coupled probes.

Rieusset Jennifer - jennifer.rieusset@univ-lyon1.f r - 0426235920 - http://carmen.univ-lyon1.fr/equipe-3-glucolipotoxicite-stress-metaboliques-et-diabetes/

Anne Bouloumie-Diehl

the stroma-vascular cells of adipose tissue

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Our approaches on human and rodent adipose tissues that combine cell sorting, confocal analyses and primary culture of adipocytes, endothelial cells, immune cells and progenitor cells are unique allowing the study of native cells and their interactions.

Key facts

Team

- Researchers : 4
- Technicians : 3
- Postdoc fellows : 1
- PhD Students : 2

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 2

International research links

- Spain
- Sweden

Keywords

- diabetes
- senescence
- adipogenesis
- endothelial cells
- stem/progenitor cells
- adipose tissue
- secretome
- inflammation
- flow cytometry
- confocal microscopy
- cell culture
- immunoselection
- molecular biology

Biological Resources

- Conditioned media from endothelial cells, macrophages, lymphocytes, progenitor cells and adipocytes from human adipose tissue
- mRNA from native endothelial cells, macrophages, lymphocytes, progenitor cells and adipocytes from human adipose tissue
- native endothelial cells, macrophages, lymphocytes, progenitor cells and adipocytes from human adipose tissue

Research Brief :

Our research is focused on the cells from the stroma-vascular fraction of the adipose tissue, i.e. endothelial cells, macrophages, T lymphocytes and progenitor cells, in human and rodent models. We study the relative contribution of the distinct cell subsets in the adipose tissue dysfunction linked with obesity and associated pathologies. The clinical and animal studies are combined with cellular (immunoselection/depletion cell sorting, 3dimensional confocal analyses, flow cytometry, primary cultures) and biochemical approaches. The projects are focused on 1) the proliferation, differentiation and reparative potentials of the adipose tissue progenitor cells, 2) the immuno-inflammatory processes in the aging adipose tissue, and 3) the modulatory role of the adipose tissue endothelium in the adipose tissue growth and inflammation.

- **Methodologies Used :**

Immunoselection/depletion cell sorting by the use of magnetic nano- and micro-beads
Flow cytometry and three dimensional confocal analyses of the adipose tissue
Primary cultures of human and murine mature adipocytes, adipose tissue endothelial cells, macrophages, lymphocytes, progenitor cells and preadipocytes.

Publications

Miranville A, Heeschen C, Sengenès C, Curat CA, Busse R, Bouloumié A (2004). Improvement of postnatal neovascularization by human adipose tissue-derived stem cells., Circulation. 110(3), 349-55

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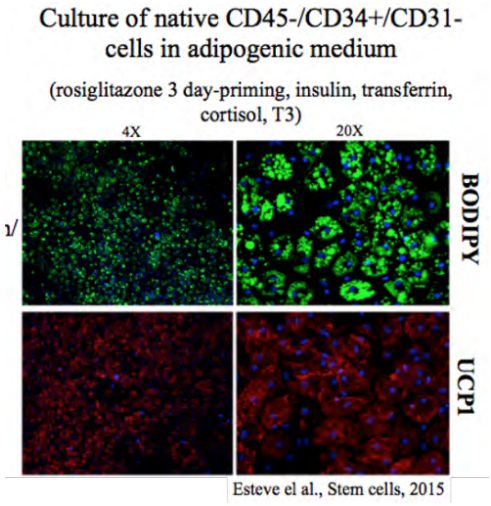
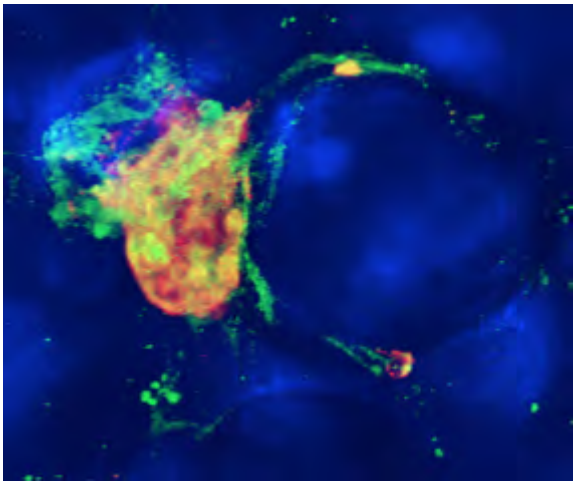
Identification of the human adipose tissue native white and brite progenitor cells



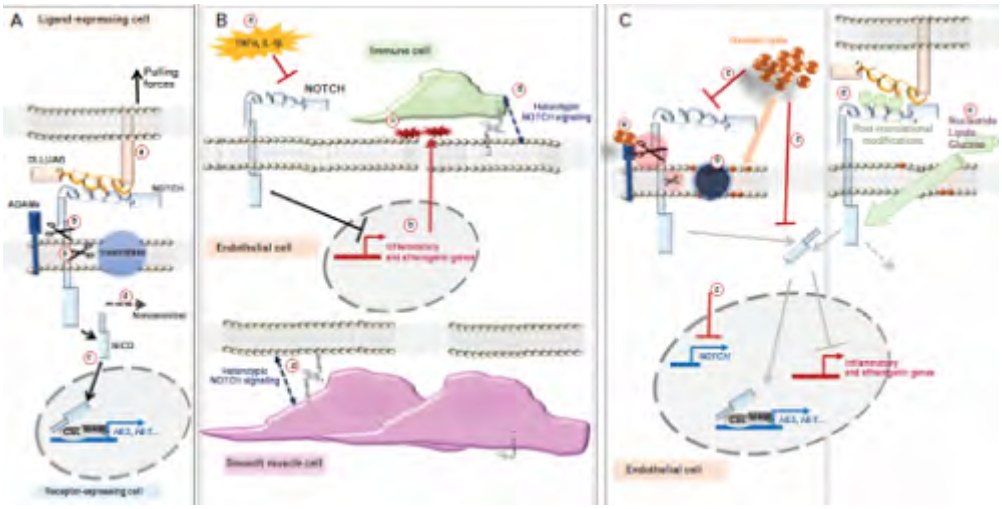
Flow cytometry of the human adipose tissue stroma-vascular cells after collagenase digestion allows the immunoselection of CD45-/ CD 34+/ CD 31- progenitor cells that can upon culture accumulate lipids in their multiple lipid droplets (BODIPY) or express the mitochondrial uncoupling protein 1 (UCP1), which are arker of mature white and brite fat cells.

Adipose tissue microenvironment and obesity



Lymphocyte T neighboring of mature adipocytes is increased with obesity . Here the immune cells are labelled in red (CD3) and green (CD45) while the adipocytes (in blue) are recognizable by their round-shaped profile.

Endothelial Notch signaling pathway and interactions with the microenvironment



(A) Dimerization of NOTCH receptor with DLL/JAG ligand, proteolytic cleavage by ADAM family proteases /g-secretase complex, NOTCH intracellular domain (NICD) translocation to nucleus, interaction with MAML/CSL and transcription of target genes.(B) Inflammation suppresses NOTCH in endothelial cells, expression of inflammatory and atherogenic mediators, immune cell recruitment, bi-directional heterotypic communication (C) Oxidized phospholipids repress NOTCH & promote endothelial activation.

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Corinne Leloup

Brain nutrient sensing and energy homeostasis

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Lionel Brétillon
Dijon

Key facts

Team

• Researchers : 5
• Technicians : 4
• Postdoc fellows : 0
• PhD Students : 1

Translational approaches

• Patents : 0
• Clinical research grants : 0
• Industry partnerships : 1

International research links

• Suisse
• Etats-Unis

Keywords

• hypothalamic glucose sensing
• obesity and diabetes
• mitochondria, fission, ROS signaling
• food intake and nervous control of energy metabolism
• astrocytes, glial networks
• Human studies on feeding behaviour
• preferences, liking/wanting, taste exploration
• Human metabolic disorders/eating disorders
• electrophysiological studies (on brain in vivo; ex-vivo; on freshly isolated islets)
• mitochondrial exploration (oxygraphy)
• freshly isolated hypothalamic cells and pancreatic islets/Ca+ imaging
• stereotaxy for brain injection
• hyperinsulinemic euglycemic clamp
• Gustatory evoked potentials

Biological Resources

• Human beings for metabolic pathologies associated with eating disorders
• in vivo/vitro hypothalamic models to study obesity and diabetes

Combination of multiple in vivo and in vitro studies to explore the detection of nutrient in the brain. (animal models) Multiple approaches (Prefquest to Gustatory evoked potentials) to study preferences and gustatory detection in metabolic pathologies with eating disorders. (Human beings)

Research Brief :

The brain participates in energy homeostasis by regulating both energy intake and metabolism. The hypothalamus in particular monitors nervous, hormonal and metabolic signals and integrates them to elicit adaptive responses. The hypothalamus is sensitive to glucose whose blood level is tightly regulated and has profound effects on some hypothalamic neurons. These hypothalamic glucose changes then participate in food intake and numerous peripheral controls, for instance insulin secretion or hepatic glucose production. Our research focuses on hypothalamic glucose sensing mechanisms, especially the detection of increased blood glucose levels, and gustatory detection in Humans and the relationships between these detections and energy homeostasis. In particular, our studies are aimed at 1) deciphering cellular and molecular mechanisms involved in hypothalamic glucose sensing (especially those of mitochondria, the role of the astroglial networks), 2) determining its importance both in physiology and pathology (obesity, diabetes) on food intake and nervous control of peripheral organs , 3) exploring similarities of the glucose sensing mechanism with the pancreatic beta-cell, and finally 4) identifying changes in gustatory nutrient sensing and preferences in metabolic human pathologies associated with changes in food intake.

• **Methodologies Used :**

Stereotaxic brain injections:drugs, viral particles or siRNA
Food intake and metabolic characterizations (functional tests for physiology exploration: refeeding, hyperinsulinemic/ eu(hypo)glycemic clamps, glucose and insuline tolerance tests, targeting the brain through carotid injection), preference/aversion and electrophysiological gustatory study through evoked potentials recording (Humans)
Mitochondrial exploration: oxygraphy (OXPHOS studies), ROS production, antioxidant defences, redox metabolism
Patch clamp recordings on acute hypothalamic brain slices and in vivo electrophysiological recordings
Ca2+ imaging on hypothalamic freshly dissociated cells
Single cell RT-PCR, qPCR, immunohistochemistry

Publications

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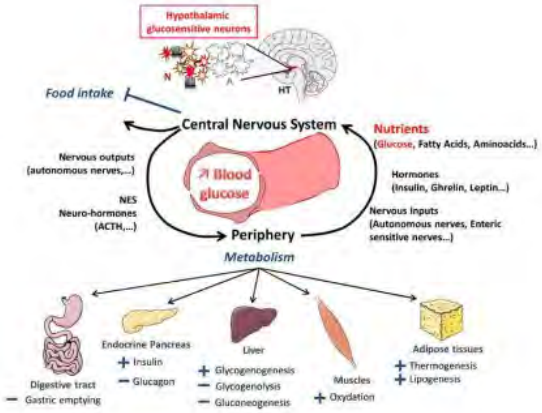
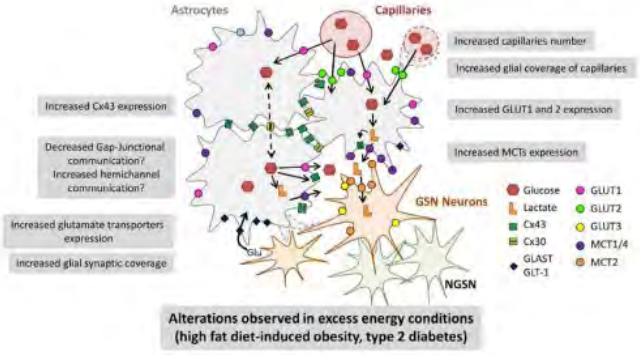
physiological responses after hypothalamic glucose detection



Major actors of hypothalamic glucose detection- Alterations in obese, diabetic models



GSN: glucosensitive neurons

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Metabolism
Nutrition

Hubert Vidal Martine Laville

Nutritional Adaptations, Environment and Diabetes

Université de Lyon 1
(Université Claude Bernard) INSA de Lyon
INRA UMR1397 Inserm UMR1060
Hubert Vidal
Lyon

Key facts

Team

• Researchers : 19
• Technicians : 6
• Postdoc fellows : 4
• PhD Students : 6

Translational approaches

• Patents : 2
• Clinical research grants : 14
• Industry partnerships : 8

International research links

• Brazil
• Canada
• Norway

Keywords

• Nutrigenomics
• overfeeding
• food pollutants
• microbiota
• metabolic flexibility
• insulin resistance
• epigenetics
• clinical investigation
• hyperinsulinemic clamp.
• microarray
• gene expression analysis

Biological Resources

• human skeletal muscle cell bank
• human muscle and adipose tissue biobanks

Translational research in nutrition and metabolic disease.

Research Brief :

The main objectives of our research program are 1) to understand at the molecular level the adaptive responses to changes in our nutritional environment and 2) to identify the potential defects in these processes that could contribute to the metabolic pathologies. To this aim, we investigate the adaptive mechanisms to metabolic stress and pollutant exposure under different experimental conditions reflecting as much as possible normal life. Based on the significant advances made over the last years, our strategy rely on 5 complementary aresearch programs:
? ?Metabolic adaptation and inflammation of fat tissues during overfeeding? to understand adipose tissue depots remodeling and to propose strategies to fight obesity and prevent its complications;
? «Adipose stem cells in healthy or pathological adipose tissues» to understand the mechanisms initiating adipose tissue alterations and inflammation which lead to the complications of obesity;
? ?Metabolic disrupters: impact of environmental pollutants in metabolic diseases? to unravel the contribution and the mechanisms of action of pollutants in triggering or amplifying metabolic diseases;
? ?Metabolic adaptations in chronic kidney disease? to define the determinants of metabolic complications, especially insulin resistance, in chronic kidney disease;
? ?Probiotics as a new strategy to fight metabolic diseases? to demonstrate that selected bacterial strains can be powerful agents to treat obese and diabetic patients.

• **Methodologies Used :**

- Nutrigenomics and gene expression analysis
- Nutritional interventions in humans and in animal models
- Micorbiota and probiotics
- Epignetics and chromatin organisation study
- Hormone signaling
- Skeletal muscle and adipose tissue cell culture

Publications

Naville D, Pinteur C, Vega N, Menade Y, Vigier M, Le Bourdais A, Labaronne E, Debard C, Luquain-Costaz C, Bégeot M, Vidal H, Le Magueresse-Battistoni B. (2013). Low-dose food contaminants trigger sex-specific, hepatic metabolic changes in the progeny of obese mice, FASEB Journal. 278(9), 3860-70

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Key facts

Team

- Researchers : 21
- Technicians : 5
- Postdoc fellows : 2
- PhD Students : 6

Translational approaches

- Patents : 2
- Clinical research grants : 6
- Industry partnerships : 6

International research links

- USA
- Netherlands
- Canada

Keywords

- Lipid
- Intestinal absorption
- Hypertriglyceridemia
- Lipoprotein
- Nutrition
- Endotoxemia
- Animal model
- Cell culture
- Lipidomics
- Clinical trial

Biological Resources

- rodent models
- in vitro models: Caco-2 cells, endothelial cells...

Marie-Caroline Michalski
Philippe Moulin

Postprandial Lipids and Lipoproteins: Regulations and Functional Impacts

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Hubert VIDAL
VILLEURBANNE

To facilitate and accelerate translational research by combining genetics, lipidomics and both in vitro and clinical experiments in order to explore lipid metabolism in patients and in healthy controls. To consider the molecular and supramolecular structures of dietary lipids in their effects.

Research Brief :

The main scientific objectives are to understand the mechanisms and the consequences of hypertriglyceridemia by studying both primary and secondary hypertriglyceridemia as well as postprandial hyperlipidemia. The team will focus on:1) How dietary lipids, through their structure and oxidation, can metabolically impact on intestinal absorption, TGRL composition and lipolysis, and the metabolic fate of lipids in the postprandial phase. The role of specific lipids present in the gut on LPS coabsorption and biology of the gut cell lienage will be considered. 2) How TGRL modified by nutrition and/or altered by abdominal obesity/diabetes or malabsorption play a role in atherothrombotic and inflammatory processes both in the fasting and postprandial phase. The role of oxygenated species derived from DHA on ischemic cardiovascular disease will be studied.3) How new genetic and epigenetic regulations interfere with TGRL lipolysis. Interactions between LPL/AV/GPIHBP1 on endothelial cells will be studied. Association studies in extreme phenotypes and segregation studies in families with unexplained familial chylomicronemia syndrome will be conducted to identify new genes involved in TG metabolism. Studies considering the role of miRNA in the regulation of lipolysis gene expression will be expended.This project will provide new dietary strategies to prevent the alterations of postprandial lipemia and identify new therapeutic targets for improving treatment of hypertriglyceridemia.

- **Methodologies Used :**

- Nutritional interventions in humans and in animal models (mice and rats).
- Cell cultures Cell biology (transwell inserts).
- Next generation sequencing (386 gene chips) applied in the field of dyslipoproteinemia
- Lipoprotein isolations and platelet aggregation.
- Endotoxemia analysis.
- Lipidomic platform analyses (HPLC, GC, GC-MS/MS, LC-MS/MS).

Publications

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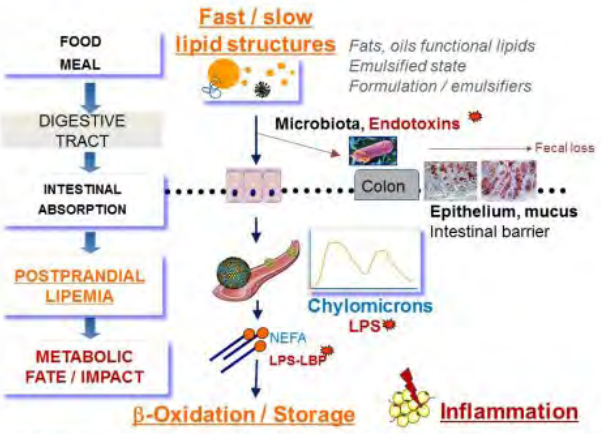
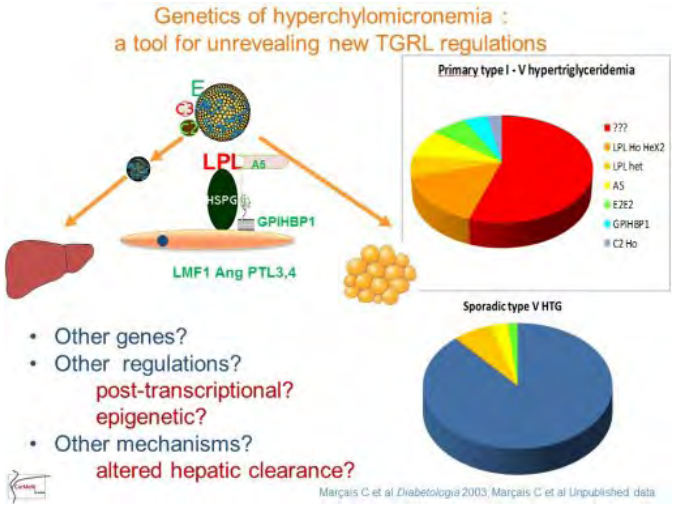
Impact of dietary lipid structures on postprandial lipemia and metabolism



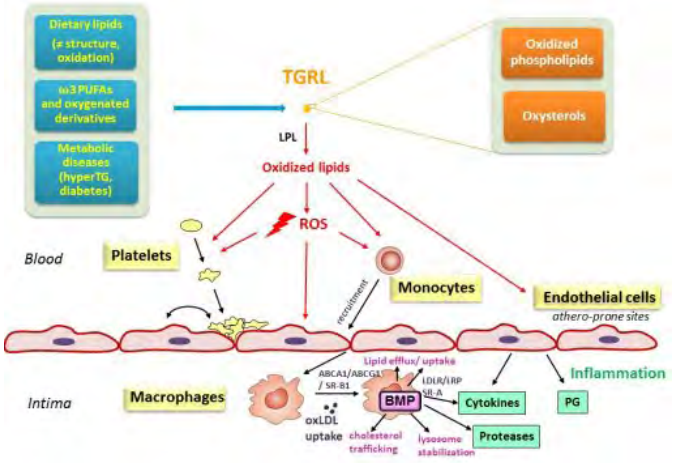
Michalski et al., *Prog Lipid Res* 2013 - Bourlieu et Michalski, *Cur Op Clin Nutr Met Care* 2015

Genetics of hyperchylomicronemia : a tool for unraveling new TG-rich lipoprotein regulations



Marçais C et al *Diabetologia* 2003, Marçais C et al Unpublished data

Functional impact of TGRL as vector of oxidized lipids on circulating cells and endothelium



Michalski Marie-Caroline - marie-caroline.michalski@insa- lyon.fr - 0472438570

Key facts

Team

- Researchers : 122
- Technicians : 52
- Postdoc fellows : 5
- PhD Students : 62

Translational approaches

- Patents : 1
- Clinical research grants : 14
- Industry partnerships : 11

Keywords

- energy metabolism
- metabolic flux
- insulin-resistance
- obesity
- food bioavailability
- physical activity assessment
- mass spectrometry
- -omic platforms
- clinical phenotyping

Biological Resources

- Blood, plasma and stool samples

CRNH Rhône Alpes

Human Nutrition Research Center

Université Claude Bernard
Lyon I
Inserm, inra, CarMen
Julie-Anne Nazare
Lyon, Grenoble, Saint-Etienne

> ***A center of excellence in human nutrition and health from preclinical to clinical research***

Research Brief :

The CRNH Rhône-Alpes is a GIP, founded in 1996 and renewed until 2020. Partners are:
Research institutes (INSERM and INRA), Universities (Lyon 1, J. Fourier in Grenoble, J. Monnet in Saint Etienne), Hospitals (Hospices Civils de Lyon, CHU Grenoble and St Etienne).
The Human Nutrition Research Center Rhône-Alpes strives to improve human nutrition and health. It develops research programs in nutrition within the framework of national, european and international research programs, working closely with industrial partners and researchers worldwide.
The association of more than 200 people from 20 hospital services, 3 universities and research units (CarMeN INSERM U1060-INRA USC 1362-INSA, INSERM U1042 and U1055, EA 4607 SNA-EPIS) makes it possible to set up studies on priority Public Health matters such as obesity, diabetes, cardiovascular diseases and malnutrition associated with chronic diseases and extreme old age.
The CRNH Rhône-Alpes is involved in all the major fields of nutrition research through very close partnerships with other CRNHs (Auvergne, Ile de France, Ouest) and with the research center of the Paul Bocuse Institute (food behaviour/experimental restaurant).
All these research strengths are associated in the CENS (European Center for Nutrition and Health): a consortium of scientists and clinicians specialized in nutrition, together with industrial partners to address health and societal challenges at an international level.

Methodologies Used :

Nutritional intervention in healthy subjects or patients and metabolic phenotyping (OGTT, clamps for insulin sensitivity determination; Bio impedancemetry, labeled water, DEXA, imaging for body composition determination)
Stable isotopes technology for substrate turnover and food bioavailability determined by mass spectrometry (GCMS, GCIRMS)
Indirect calorimetry, doubly labeled water, actimetry and questionnaires for energy expenditure measurement
Muscle and/or adipose tissue biopsies for genomics and proteomics analyses
Access to MRI and PET MRI

Publications

Bergouignan A, Momken I, Schoeller DA, Normand S, Zahariev A, Lescure B, Simon C, Blanc S (2010). Regulation of energy balance during long-term physical inactivity induced by bed rest with and without exercise training., The Journal of clinical endocrinology and metabolism. 95(3), 1045-53

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Sforza E, Boissier C, Martin MS, Feasson S, Barthélémy JC, Roche F (2013). Carotid artery atherosclerosis and sleep disordered breathing in healthy elderly subjects: the Synapse cohort., Sleep medicine. 14(1), 66-70

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Alligier M, Gabert L, Meugnier E, Lambert-Porcheron S, Chanseaume E, Pilleul F, Debard C, Sauvinet V, Morio B, Vidal-Puig A, Vidal H, Laville M (2013). Visceral fat accumulation during lipid overfeeding is related to subcutaneous adipose tissue characteristics in healthy men., The Journal of clinical endocrinology and metabolism. 98(2), 802-10

Allirot X, Saulais L, Seyssel K, Graeppi-Dulac J, Roth H, Charrié A, Drai J, Goudable J, Blond E, Disse E, Laville M (2013). An isocaloric increase of eating episodes in the morning contributes to decrease energy intake at lunch in lean men., Physiology & behavior. 110-111(), 169-78

Key facts

Team

- Researchers : 2
- Technicians : 3
- Postdoc fellows : 5
- PhD Students : 2

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 1

Keywords

- Microbiota
- Microbiome
- Probiotics
- Lactobacilli
- Drosophila
- Growth
- Nutrition
- gnotobiology
- genetics
- Functional genomics
- nutritional manipulation

Biological Resources

- Library of Lactobacilli isolates for functional screening
- in vivo animal models for functional screening of candidate probiotics

François Leulier

Functional genomics of host/intestinal bacteria interactions

Université de Lyon 1
(Université Claude Bernard) Ecole Normale Supérieure de Lyon
CNRS
Vincent Laudet
Lyon

> ***We have developped an original model to study host/microbiota interaction which has a great potential for functional and mechanistic studies thanks to its simplicity and genetic tractability***

Research Brief :

Metazoans establish reciprocal interactions with their commensal bacterial communities (i.e microbiota). Despite recent progress, a clear view of the physiological benefits associated with host/microbiota relationship remains elusive. Hence the molecular mechanisms through which the microbiota exerts its beneficial influences are still largely undefined. Hence, the goals of our research programs are two folds:
(1) Decipher the molecular dialogue governing the mutualistic interaction between intestinal bacteria and their host. To this end, we are using an animal model, Drosophila melanogaster and one of its natural commensal, Lactobacillus plantarum. We are developing a multiscale functional approach to identify the mechanisms that underly their mutualistic relationship by initially focusing on L.plantarum mediated host juvenile growth promotion. Our approaches aim at identifying both the bacterial and host genetic networks required to sustain a mutualistic relationship. We are also translating our discoveries to mammalian models by studying the impact of selected strains of L.plantarum on mice juvenile growth.
(2) Identify and characterize new potential Lactobacilli probiotic strains beneficial to host biology by mean of in vivo functional screens using the Drosophila model and tailored bacterial experimental evolution strategies to generate "optimized" probiotic strains.

• Methodologies Used :

Drosophila and Mouse gnotobiology
Functional genomics
Drosophila and Lactobacilli forward and reverse genetics
Experimental Evolution.
Nutritional manipulation

Publications

Leulier F, Lemaitre B (2008). Toll-like receptors--taking an evolutionary approach., Nature reviews. Genetics. 9(3), 165-78

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Combe BE, Defaye A, Bozonnet N, Puthier D, Royet J, Leulier F (2014). Drosophila Microbiota Modulates Host Metabolic Gene Expression via IMD/NF-?B Signaling., PloS one. 9(4), e94729

Leulier François - francois.leulier@ens-lyon.fr

Uwe Schlattner

LBFA - Laboratoire de Bioénergétique Fondamentale et Appliquée

Université Grenoble Alpes
Inserm U1055
Uwe Schlattner
Grenoble

Key facts

Team

- Researchers : 19
- Technicians : 11
- Postdoc fellows : 1
- PhD Students : 9

Translational approaches

- Patents : 9
- Clinical research grants : 2
- Industry partnerships : 3

International research links

- USA
- UK
- Spain

Keywords

- energy homeostasis
- mitochondria
- AMP-activated protein kinase
- permeability transition pore
- nutrition
- interactomics
- proteomics
- metabolic analysis
- microscopy
- animal models

Biological Resources

- recombinant proteins
- cell cultures
- primary cells (hepatocytes, cardiomyocytes)
- animal models (rats, transgenic mice)

Research at LBFA is integrating molecular, cellular, whole organism and clinical research in bioenergetics.

Research Brief :

The main focus of LBFA research is on energy homeostasis and mitochondrial physiology, as well as their dysfunction in human disease. This includes projects on cell signaling, cell compartmentation, efficiency of cellular ATP generation, regulation of cell death, exercise and nutrition. LBFA research is organized in three axes:
(1) "Energy signaling and systems bioenergetics" (U Schlattner) is working on molecular mechanisms in the regulation of cellular energy state and energy homeostasis, in particular structure, function and signaling of AMP-activated protein kinase, topology, dynamics and function of mitochondrial microcompartments, and spatio-temporal dynamics of cellular energetics.
(2) "Mitochondria and cell death" (E. Fontaine) is working on mitochondria, oxidative phosphorylation, cell death (mitochondrial permeability transition), and pathological energy disorders.
(3) "Metabolism, nutrition & exercise" is working on nutritional end exercise effects on metabolic regulation, nutritional status, nutrition of the elderly and nutritional supplements.
LBFA also develops and applies integrative approaches, including innovative technologies (e.g. in vivo imaging with intracellular sensors, interactomics) and mathematical modeling within the Federative Structure ?Environmental and Systems Biology (BEeSy).

- **Methodologies Used :**

Recombinant protein expression, purification and biochemical/biophysical characterization.
Experimental models of nutritional regimes, metabolic or energy disorders in vitro and in vivo (cell culture, mice, rats)
Proteomics (2D-PAGE etc., mass spectrometry) and transcriptomics (RT-PCR, microarrays)
Interactomics (innovative yeast-two-hybrid systems, surface plasmon resonance)
Microscopy (fluorescence, confocal)
Metabolic and metabolite analysis (metabolic cage with gas exchange and movement analysis, cell perifusion, oxygraphy, HPLC)

Publications

Schlattner U, Tokarska-Schlattner M, Ramirez S, Tyurina YY, Amoscato AA, Mohammadyani D, Huang Z, Jiang J, Yanamala N, Seffouh A, Boissan M, Epand RF, Epand RM, Klein-Seetharaman J, Lacombe ML, Kagan VE. (2013). Dual function of mitochondrial Nm23-H4 protein in phosphotransfer and intermembrane lipid transfer: a cardiolipin-dependent switc, J Biol Chem. 288(1), 111-21

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Boissan M, Montagnac G, Shen Q, Griparic L, Guitton J, Romao M, Sauvonnet N, Lagache T, Lascu I, Raposo G, Desbourdes C, Schlattner U, Lacombe ML, Polo S, van der Bliek AM, Roux A, Chavrier P. (2014). Membrane trafficking. Nucleoside diphosphate kinases fuel dynamin superfamily proteins with GTP for membrane remodeling., Science. 344(6191), 1510-5

Ramírez Ríos S, Lamarche F, Cottet-Rousselle C, Klaus A, Tuerk R, Thali R, Auchli Y, Brunisholz R, Neumann D, Barret L, Tokarska-Schlattner M, Schlattner U. (2014). Regulation of brain-type creatine kinase by AMP-activated protein kinase: interaction, phosphorylation and ER localization., Biochim Biophys Acta. 1837(8), 1271-83

Kagan VE, Jiang J, Huang Z, Tyurina YY, Desbourdes C, Cottet-Rousselle C, Dar HH, Verma M, Tyurin VA, Kapralov AA, Cheikhi A, Mao G, Stolz D, St Croix CM, Watkins S, Shen Z, Li Y, Greenberg ML, Tokarska-Schlattner M, Boissan M, Lacombe ML, Epand RM, Chu CT, Mallampalli RK, Bay?r H, Schlattner U. (2015). NDPK-D (NM23-H4)-mediated externalization of cardiolipin enables elimination of depolarized mitochondria by mitophagy., Cell Death Differ. 23(7), 1140-51

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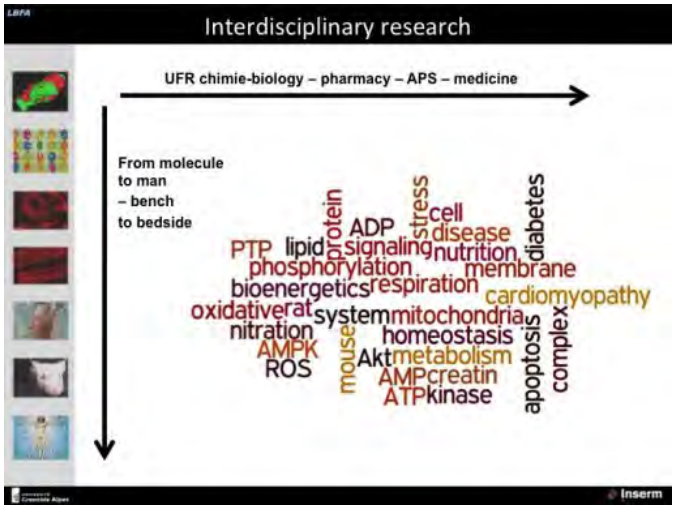
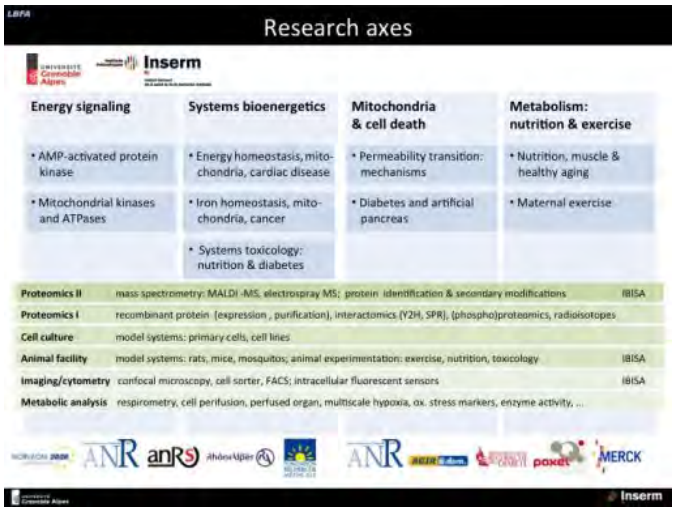
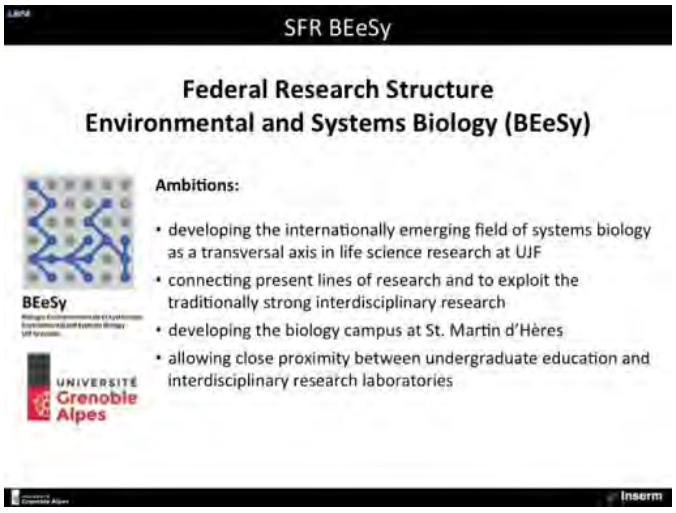
LBFA interdisciplinary research



LBFA research axes



SFR Environnemental and Systems Biology



Schlattner Uwe - uwe.schlattner@univ-grenoble-a lpes.fr - 0699255966 - http://www-lbfa.ujf-grenoble.fr

Key facts

Team

- Researchers : 12
- Technicians : 6
- Postdoc fellows : 2
- PhD Students : 3

Translational approaches

- Patents : 2
- Clinical research grants : 2
- Industry partnerships : 3

International research links

- University of Graz (Prof. Rudolf Zechner)
- Karolinska Institute (Prof. Peter Arner, Prof. Mikael Ryden)
- Oslo University (Prof. Arild Rustan)

Keywords

- dietary intervention
- physical exercise
- calorie restriction
- insulin resistance
- adipokines
- inflammation
- fatty acid metabolism
- lipolysis
- skeletal muscle
- adipose tissue
- Obesity
- gene expression profiling
- lipid metabolism
- transgenic mice
- human cell primary cultures
- Functional genomics

Biological Resources

- human adipose tissue biobanks
- primary cultures of human fat and skeletal muscle cells

Cedric Moro Dominique Langin

Obesity Research Laboratory

Université de Toulouse 3
(Université Paul Sabatier)
Inserm UMR1048
Angelo Parini
Toulouse

Our translational approach goes from discovery of novel pathways and regulations in clinical studies to molecular deciphering of the mechanisms in human cell and transgenic mouse models, thus ascertaining relevance of our projects in the context of human obesity and its metabolic consequences.

Research Brief :

The Obesity Research Laboratory works on the consequences of the excess of fat mass observed in obesity and aims at understanding the biological determinants and molecular mechanisms of obesity-related metabolic complications with a special emphasis on type 2 diabetes.

We have studied novel aspects of fatty acid metabolism in adipose tissue and skeletal muscle as well as the links between metabolic, inflammatory and fibrotic pathways and their relationship with lipotoxicity and insulin resistance. Using a bedside-to-bench approach, we have shown that modulation of adipose tissue and skeletal muscle lipolysis impacts on fat oxidation, lipotoxicity and insulin sensitivity. Studies in mice and humans revealed that pharmacological (inhibition of lipolysis, treatment with natriuretic peptides) and lifestyle (physical exercise, low calorie diet) interventions improve adipose tissue and skeletal muscle function as well as whole-body insulin sensitivity. In fat cells, inhibition of lipolysis or activation of fatty acid oxidation shows beneficial effects by limiting fatty acid release into blood circulation and by intrinsic modulation of glucose metabolism. In skeletal muscle, the regulation of intramyocellular triglyceride metabolism by lipases and of fatty acid oxidation by natriuretic peptides may be protective against the deleterious role of excess circulating fatty acids in obesity.

- **Methodologies Used :**

Our overall objective is now to decipher the cellular and molecular mechanisms associating fatty acid and glucose metabolisms at tissue and whole body levels and to evaluate the therapeutic potential of the inhibition of adipose tissue lipolysis and activation of skeletal muscle and adipose tissue fatty acid oxidation.
These topics are tackled by approaches combining clinical studies in humans (obesity, dietary interventions and physical activity), phenotyping of transgenic mouse models and studies on cellular models (primary cultures of human fat and skeletal muscle cells).

Publications

Engeli S, Birkenfeld AL, Badin PM, Bourlier V, Louche K, Viguerie N, Thalamas C, Montastier E, Larrouy D, Harant I, de Glisezinski I, Lieske S, Reinke J, Beckmann B, Langin D, Jordan J, Moro C (2012). Natriuretic peptides enhance the oxidative capacity of human skeletal muscle, J. Clin. Invest.. 122(12), 4675

Girousse A, Tavernier G, Valle C, Moro C, Mejhert N, Dinel AL, Houssier M, Roussel B, Besse-Patin A, Combes M, Mir L, Monbrun L, Bézaire V, Prunet-Marcassus B, Waget A, Vila I, Caspar-Bauguil S, Louche K, Marques MA, Mairal A, Renoud ML, Galitzky J, Holm C, Mouisel E, Thalamas C, Viguerie N, Sulpice T, Burcelin R, Arner P, Langin D (2013). Partial inhibition of adipose tissue lipolysis improves glucose metabolism and insulin sensitivity without alteration of fat mass, PLoS Biol. 11(2), e1001485

Vila IK, Badin PM, Marques MA, Monbrun L, Lefort C, Mir L, Louche K, Bourlier V, Roussel B, Gui P, Grober J, ?tich V, Rossmeislová L, Zakaroff-Girard A, Bouloumié A, Viguerie N, Moro C, Tavernier G, Langin D (2014). Immune cell Toll-like receptor 4 mediates the development of obesity- and endotoxemia-associated adipose tissue fibrosis, Cell Rep. 7(4), 1116

Caspar-Bauguil S, Kolditz CI, Lefort C, Vila I, Mouisel E, Beuzelin D, Tavernier G, Marques MA, Zakaroff-Girard A, Pecher C, Houssier M, Mir L, Nicolas S, Moro C, Langin D (2015). Fatty acids from fat cell lipolysis do not activate an inflammatory response but are stored as triacylglycerols in adipose tissue macrophages, Diabetologia. 58(11), 2627

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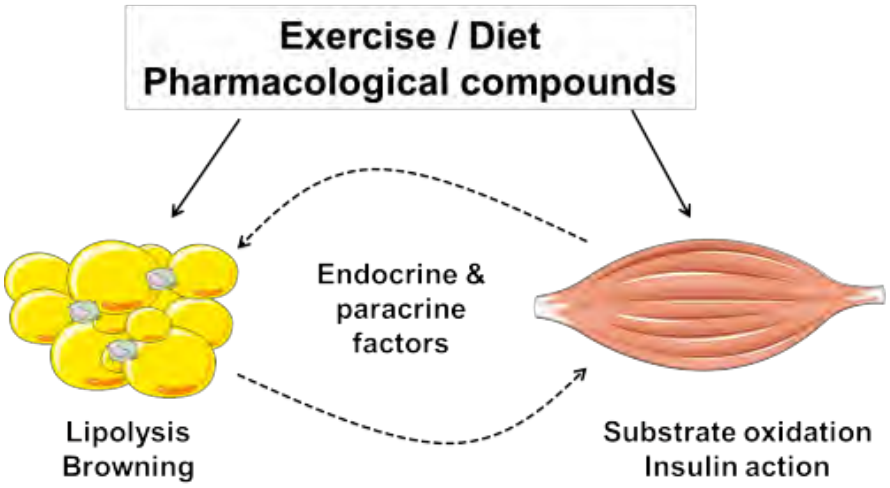
Overview Obesity Research Laboratory



Moro Cedric - cedric.moro@inserm.fr - 0561325626 - http://www.i2mc.inserm.fr

Key facts

Team

- Researchers : 6
- Technicians : 3
- Postdoc fellows : 3
- PhD Students : 4

Translational approaches

- Patents : 2
- Clinical research grants : 2
- Industry partnerships : 1

Keywords

- Atherosclerosis
- High Density Lipoproteins (HDL)
- Phosphoinositide 3-kinase (PI3K)
- signaling
- inflammation
- mitochondria.
- mice models of atherosclerosis and endovascular lesions
- Lipoproteins analysis

Laurent Martinez

High Density Lipoproteins (HDL) and PI3K Signaling in Atherosclerosis

Université de Toulouse 3
(Université Paul Sabatier)
INSERM UMR1048
Angelo Parini
Toulouse

Our projects aim to identify new molecular mechanisms and lipid signaling pathways involved in HDL-mediated atheroprotection, in order to determine new targets for the prevention and treatment of Coronary Artery Diseases (CAD).

Research Brief :

Atherosclerosis is a chronic inflammatory pathogy of the vascular wall, in large part due to the accumulation of macrophages foam cells without adequate removal of cholesterol by High Density Lipoproteins (HDL). Lipid deposits lead to the formation of atherosclerotic plaques that damage the vascular wall and can be further complicated by plaque disruption and thrombosis. Our project, developed around 3 axes, is focused on the metabolic and vascular atheroprotective functions of HDL and on phosphoinositide 3-kinase lipid signaling pathways in atherosclerosis:
1°) HDL-mediated Reverse Cholesterol Transport (RCT).
The protective effect of HDL against atherosclerosis is mostly attributed to their central functions in RCT. In this context, we identified a metabolic sequence in which apolipoprotein A-I (apoA-I) binds to ATP-synthase (F1-ATPase) at the surface of hepatocytes, triggering ATP hydrolysis. The generated ADP interacts with the P2Y13 receptor, which then stimulates HDL uptake. We currently evaluate the relevance of this HDL-uptake pathway in atherosclerosis and its regulation.
2°) New signaling pathways in vascular wall protection.
We have demonstrated that the gamma isoform of PI3K plays an essential role in inflammatory processes of vascular wall. We are now studying PI3K and apoA-I induced-signaling pathway in the prevention of vascular dammages.
3°) Identification of genotypic or biological determinants of HDL levels and functions.

- **Methodologies Used :**

1/ Mice models of atherosclerosis: atherosclerotic lesions in aortic roots sections and « en face » analysis.
2/ Lipoproteins metabolism: Lipoproteins uptake by cell and liver, plasma lipoprotein analysis, gallbladder cannulation.
3/ Mice models of endovascular lesions: arterial reendothelization and intimal hyperplasia.
4/ Primary cell culture (mice hepatocytes and aortic SMC), fluorescent proteins production and labelling.

Publications

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Key facts

Team

- Researchers : 5
- Technicians : 4
- Postdoc fellows : 1
- PhD Students : 2

Translational approaches

- Patents : 5
- Clinical research grants : 2
- Industry partnerships : 4

Keywords

- insulin resistance
- intestinal microbiota
- metagenomique
- heart failure
- lipids
- Gut to brain axis
- Enteroendocrine hormones
- metagenomics biostatistics
- cell culture
- Glucose turnover in vivo
- immunological phenotyping
- heart function phenotyping

Biological Resources

- Human liver gene expression and metagenomic in feces (NAFLD patients), human colonic and ileon biopsies
- Tailor made animal models of diabetes, obesity, heart failure. Caco2 cells, intestinal lipid transport

Rémy Burcelin

Intestinal Risk factors, diabetes, dyslipidemia

Université de Toulouse 3
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Inserm U1048
Angelo Parini
Toulouse

We described molecular mechanisms as risk factors within the gut microbiota to intestinal functions i.e. neuroendocrine/immune/lipids responsible for control of metabolism and heart function. From these discoveries we set biotech companies to treat and prevent cardiometabolic diseases

Research Brief :

Determine molecular mechanisms controlling glycemia/dyslipidemia. We demonstrated the first that 1. GLUT2 and the GLP-1 receptor are molecular components of an enteric system, which detects blood glucose, that is connected to the brain via the enteric nerves. It regulates brain GLP-1 signaling and muscle glucose utilization, hepatic glucose production, insulin/glucagon secretion, and vascular blood flow. We defined this new physiological concept : The gut brain anticipatory axis and showed its impairment during diabetes, therefore setting the basis of new therapeutic strategies to treat diabetes/dyslipidemia. In the quest of the regulatory mechanisms we identified that intestinal microbiota produces factors (Metafactors, as lipopolysaccharides and bacterial DNA) responsible for inflammation, insulin resistance, hepatic lipid overload, and adipose tissue development. We are studying the molecular interactions between the Metafactors and the host for the control of glycemia, dyslipidemia, hepatic and vascular diseases. This involves deciphering 1. new metafactors (biomarkers for prediction/diagnosis/stratification). 2- eukaryotic targets of metafactors, 3. the enteric-immune system in the development of vaccine strategies, 4- molecular mechanisms in enterocytes responsible for metafactor absorption 5. The regulatory role of enteroendocrine hormones (GLP-1) on the anticipatory metabolic reflex. Patents are filed and biotech companies funded (Physiogenex SAS, Vaiomer SAS)

- **Methodologies Used :**

- State of the art techniques unique in France to study in vivo in the awake free moving mouse glucose (tracers) and vascular homeostasis (ultrasonic probe) simultaneously with brain infusate to respect the integrity of the physiological systems and to address molecular issues.
- Vagus nerve recording.
- Blood hormone biochemistry.
- Metagenomique, bioinformatique, biostatistics metafactors secretome (secreted bacterial product library)
- Accurate immunological phenotyping (FACS, lymphocyte transfer, confocal analyses?)
- Lipidology, enteric cell culture, molecular fluorescent tools for the analysis of lipid handing

Publications

Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, Bastelica D, Neyrinck AM, Fava F, Tuohy KM, Chabo C, Waget A, Delmée E, Cousin B, Sulpice T, Chamontin B, Ferrières J, Tanti JF, Gibson GR, Casteilla L, Delzenne NM, Alessi MC, Burcelin R (2007). Metabolic endotoxemia initiates obesity and insulin resistance., Diabetes. 56(), 1761-72

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Pomie C, Blasco-Baque V, Klopp P, Nicolas S, Waget A, Loubieres P, Azalbert V, Puel A, Lopez F, Dray C, Valet P, Lelouvier B, Servant F, Courtney M, Amar J, Burcelin R, Garidou L (2016). Triggering the adaptive immune system with commensal gut bacteria protects against insulin resistance and dysglycemia, Molecular Metabolism. 5(), 403

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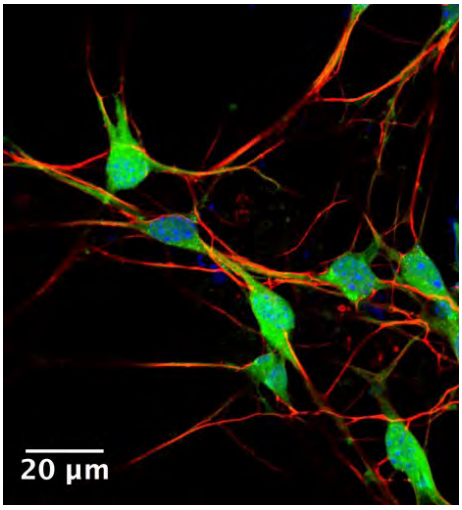
Blasco-Baque V, Garidou L, Pomie C, Escoula Q, Loubieres P, Le Gall-David S, Lemaitre M, Nicolas S, Klopp P, Waget A, Azalbert V, Colom A, Bonnaure-Mallet M, Kemoun P, Serino M, Burcelin R (2016). Periodontitis induced by Porphyromonas gingivalis drives periodontal microbiota dysbiosis and insulin resistance via an impaired adaptive immune response, Gut. 66(), 872

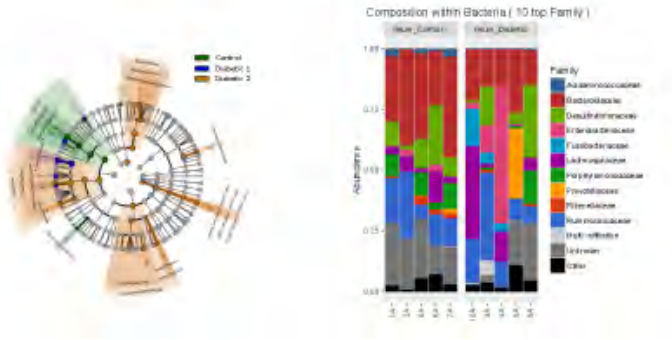
Grasset E, Puel A, Charpentier J, Collet X, Christensen JE, Terce F, Burcelin R (2017). A Specific Gut Microbiota Dysbiosis of Type 2 Diabetic Mice Induces GLP-1 Resistance through an Enteric NO-Dependent and Gut-Brain Axis Mechanism, Cell Metabolism. 25(), 1075

Entertic neurons



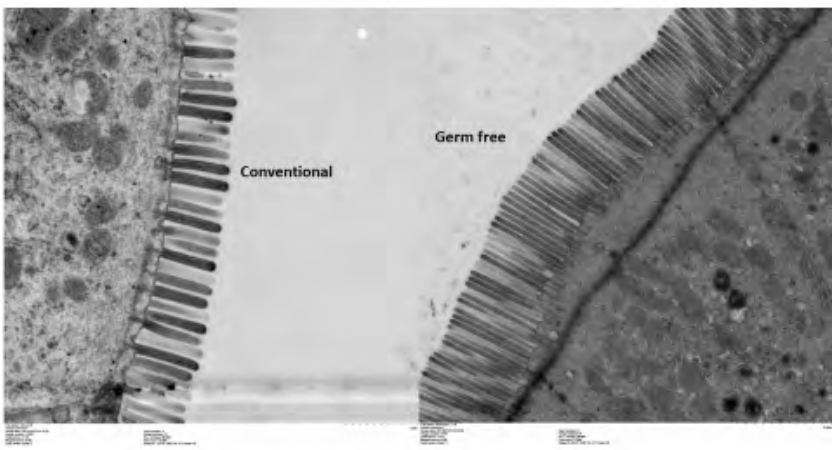
we are studying the molecular mechanisms through which the gut microbial risk factors control enteric functions such as NO production in response to GLP1

16S rDNA Metagenomic analyses



from the sequencing of gut and tissue microbiota we identify bacterial taxons differentially present within tissues.

Intestinal vili from germ free mice and conventional



Burcelin Rémy - remy.burcelin@inserm.fr - +33 (5)61325614 - http://www.i2mc.inserm.fr/index.php/fr/equipes-de-recherche/equipe-2

Key facts

Team

- Researchers : 9
- Technicians : 3
- Postdoc fellows : 1
- PhD Students : 5

Translational approaches

- Patents : 4
- Clinical research grants : 2
- Industry partnerships : 3

Keywords

- obesity
- diabetes
- adipokines
- apelin
- ageing
- rare diseases
- HMGB1
- SHP2
- mouse
- mitochondria exploration
- gene expression
- cell culture
- functional genomics
- pharmacological studies
- signal transduction
- lipid and glucid metabolism

Biological Resources

- primary -culture of adipocytes, hepatocytes (human, mouse)
- stable and transient transfections
- transgenic mouse models
- murine adipocyte (3T3F442A, SGBS) and muscle (C2C12) cell lines

Philippe Valet

Adipocyte secretions, obesities and associated diseases

Université de Toulouse 3
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Inserm U1048
Angelo Parini
Toulouse

We are investigating adipokines from molecular studies up to a potential use as pharmacological targets for obesity/diabetes in humans.

Research Brief :

Our research activity focuses on adipocyte bioactive secretions in normal and obese states and their involvement in obesity associated disorders. Metabolic alterations can occur in the way how tissues/organs behave when dealing with physiological adaptation (physical exercise, overweight), loss of response (insulin-resistance, low grade inflammation, ageing, steatosis) or disease (obesity, diabetes, rare diseases, cancer). Every key tissue in regard to energy metabolism (adipose, liver, muscle) is able to release bioactive molecules (adipokines, myokines?) acting locally or through the entire body. Our expertise in the field of adipocyte/myocyte energy metabolism as well as in the study of adipokines led us to identify original candidates involved in the use of energy substrates, to study their regulations, their metabolic actions in normal/altered situations and settle clinical trial devoted to the proof of concept in humans. Our will is to bring new clues to the question of the involvement of such cell secretory products in the dysregulations observed during metabolic diseases. We identify relevant secreted candidates as well as pertinent cellular targets leading to original pharmacological development and, thus, to improve therapeutic approaches of metabolic diseases.

- **Methodologies Used :**

Lipids and glucose metabolism (in vitro & in vivo)
Phospholipids biochemistry
Pharmacological studies in vitro and in vivo
Functionnal genomics in mouse
Mitochondria exploration

Publications

C. DRAY, C. KNAUF, D. DAVIAUD, A. WAGET, M. BULÉON, J. BOUCHER, P. CANI, C. ATTANE, C. GUIGNÉ, C. CARPÉNÉ, R. BURCELIN, I. CASTAN-LAURELL & P. VALET. (2008). Apelin stimulates glucose utilization in normal and obese insulin-resistant mice., Cell Metab.. 8(), 437-445

C. ATTANÉ, C. FOUSSAL, S. LE GONIDEC, A. BENANI, D. DAVIAUD, E. WANECQ, M. GUZMAN-RUIZ, C. DRAY C, C. RANCOULE, V. BEZAIRE, M. RUIZ-GAYO, T. LEVADE, R. BURCELIN, L. PÉNICAUD, P. VALET & I. CASTAN-LAURELL. (2012). Chronic apelin treatment stimulates fatty acid oxidation and mitochondrial biogenesis in muscle of insulin resistant mice, Diabetes. 68(), 635-644

M. TAJAN, T. CADOUDAL, A. BATUT, S. DELERUYELLE, S. LE GONIDEC, C. SAINT LAURENT, M. VOMSCHEID, E. WANECQ, K. TREGUER, A . DE ROCCA SERRA-NEDELEC, C. VINEL, M.A. MARQUES, J. POZZO, O. KUNDUZOVA , J.P. SALLES, M. TAUBER, P.RAYNAL, H. CAVE, T. EDOUARD, P. VALET & A. YART (2014). LEOPARD syndrome-associated SHP2 mutation confers leanness and protection from diet-induced obesity, Proc. Nat. Acad. Sci.. 111(), E4494-E4503

S. LE GONIDEC, C. CHAVES-ALMAGRO, Y. BAI, A. SMITH, E. WANECQ, H. PRATS, B. KNIBIEHLER, L.S. BARAK, M.G. CARON, P. VALET, Y. AUDIGIER & B. MASRI. (2017). Anti-angiogenic activity of Protamine relies on apelin receptor antagonism, Faseb J.. (),

Y.Y. WANG, C. ATTANE, D. MILHAS, B. DIRAT, S. DAUVILLIER, A. GUERARD, J GILHODES, I. LAZAR , N. ALET, V. LAURENT, S. LE GONIDEC, D. BIARD, C. HERVE, F. BOST, G.S. REN, F. BONO, G. ESCOURROU, M. PRENKI, L. NIETO, P. VALET & C. MULLER. (2017). Mammary adipocytes stimulate breast cancer invasion through metabolic remodeling of tumor cells., J. Clin. Invest. Insight.. 4(), e87489

P. GOURDY, L. CAZALS, C. THALAMAS, A. SOMMET, F. CALVAS, M. GALITZY, C. VINEL, C. DRAY, H. HANAIRE, I. CASTAN-LAURELL & P. VALET (2018). Apelin administration improves insulin sensitivity in overweight men: a randomised trial, Diabetes Obes. Metab.. 20(), 157

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Louis Casteilla

Adipose tissue plasticity

Université de Toulouse 3
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Louis Casteilla
Toulouse

Key facts

Team

- Researchers : 9
- Technicians : 3
- Postdoc fellows : 1
- PhD Students : 3

Translational approaches

- Patents : 1
- Clinical research grants : 1
- Industry partnerships : 0

Keywords

- regeneration
- redox metabolism
- stroma
- adipose tissue
- cell therapy
- mesenchymal stem cell
- 3D whole tissue imaging (spectral analysis)
- cytometry
- cell expansion
- animal model for cell transplantation
- primary culture

Biological Resources

- transgenic mice
- biobanks of ASC

We are one of the rare team in the world with a double expertise in adipose tissue biology and regenerative medicine.

Research Brief :

Adipose tissue (AT) displays great plasticity and interests a large scientific community working not only on obesity epidemic but also on plastic and reconstructive surgery and regenerative medicine. The discovery that AT hosts a large pool of adipose derived stroma/stem cells (ASC) suitable for cell transplantation largely boosted this field, in which we are one of the world leaders (we published the 1st clinical trial on ASC transplantation in critical limb ischemia). ASC effects are mediated through their multipotent differentiation and mimicry potentials as well as their strong paracrine and immune-modulatory activity. We also showed that ASC egress from AT under immune/inflammatory stimuli suggesting their role in other tissues. Beside ASC, the importance of immune cells in AT physiology makes them a preponderant determinant of AT homeostasis. Recently, we showed that AT hosts a specific endogenous hematopoietic process, that generate immune cells contributing to tissue remodelling after lesion. Our hypothesis is that AT is a reservoir of regenerative and recruitable mesenchymal and immune cells and more particularly that ASC, through their pleiotropic effects, behave as orchestra conductor of stroma controlling proper tissue homeostasis.

- **Methodologies Used :**

Primary culture,
Cell transplantation,
Cell and 3D whole tissue imaging (spectral analysis),
Cytometry (multistaining analysis, cell sorting),
cell biology,
biochemistry (redox metabolism),
Animal models
molecular biology (microarray, Q RT-PCR...)

Publications

Gil-Ortega M, Garidou L, Barreau C, Maumus M, Breasson L, Tavernier G, García-Prieto CF, Bouloumié A, Casteilla L, Sengenès C. (2013). Native adipose stromal cells egress from adipose tissue in vivo: evidence during lymph node activation., Stem Cells. 31(7), 1309-20

Bura A, Planat-Benard V, Bourin P, Silvestre JS, Gross F, Grolleau JL, Saint-Lebese B, Peyrafitte JA, Fleury S, Gadelorge M, Taurand M, Dupuis-Coronas S, Leobon B, Casteilla L. (2014). Phase I trial: the use of autologous cultured adipose-derived stroma/stem cells to treat patients with non-revascularizable critical limb ischemia., Cytotherapy. 5(7), 847-56

Carrière A, Jeanson Y, Berger-Müller S, André M, Chenouard V, Arnaud E, Barreau C, Walther R, Galinier A, Wdziekonski B, Villageois P, Louche K, Collas P, Moro C, Dani C, Villarroya F, Casteilla L. (2014). Browning of white adipose cells by intermediate metabolites: an adaptive mechanism to alleviate redox pressure., Diabetes. 63(10), 3253-65

Ngkelo A, Richart A, Kirk JA, Bonnin P, Vilar J, Lemitre M, Marck P, Branchereau M, Le Gall S, Renault N, Guerin C, Ranek MJ, Kervadec A, Danelli L, Gautier G, Blank U, Launay P, Camerer E, Bruneval P, Menasche P, Heymes C, Luche E, Casteilla L, Cousin B, Rodewald HR, Kass DA, Silvestre JS. (2016). Mast cells regulate myofilament calcium sensitization and heart function after myocardial infarction., J Exp Med. 213(7), 1353-74

Barreau C, Labit E, Guissard C, Rouquette J, Boizeau ML, Gani Koumassi S, Carrière A, Jeanson Y, Berger-Müller S, Dromard C, Plouraboué F, Casteilla L, Lorsignol A. (2016). Regionalization of browning revealed by whole subcutaneous adipose tissue imaging., Obesity (Silver Spring). 16(2), 245-57

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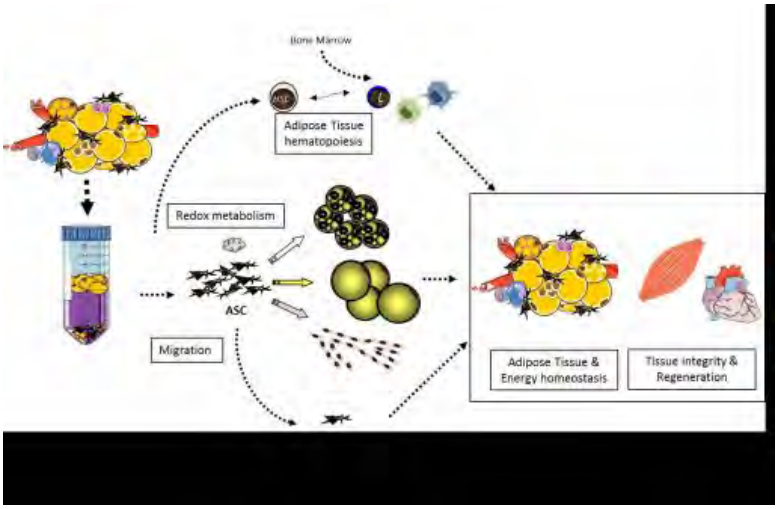
Role of ASC and adipose tissue derived immune cells in repair processes



Adipose Tissue (AT) is a reservoir of both Adipose Stromal Cells (ASC) and hematopoietic stem cells (HSC). ASCs differentiation potentials are controlled at least in part by redox metabolism, and are able to migrate to other organs under specific signals. AT-HSC generate immune cells involved in the control of AT-homeostasis and tissue remodelling after lesion. AT may thus be considered as a reservoir of regenerative and recruitable stromal and immune cells that control tissue homeostasis.

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Key facts

Team

• Researchers : 6
• Technicians : 2
• Postdoc fellows : 0
• PhD Students : 2

Translational approaches

• Patents : 1
• Clinical research grants : 1
• Industry partnerships : 3

International research links

• Italy (Dr. Laura Silvestri, San Raffaele Scientific Institute, Milan)
• Austria (Dr. Igor Theurl, Medical University of Innsbruck, Innsbruck)
• USA (Pr. Tomas Ganz, UCLA, Los Angeles & Pr. Herbert Lin, Massachusetts General Hospital, Harvard)

Keywords

• erythroferrone
• matriptase-2
• hemochromatosis
• hepcidin
• iron metabolism
• tissue iron quantification
• in vitro gene overexpression and silencing
• in vitro recombinant protein production
• mRNA and protein expression studies
• mouse models of iron disorders

Biological Resources

• mouse models of iron overload disorders

Marie-Paule Roth

Genetics and regulation of iron metabolism

Université Paul Sabatier
Toulouse III
Inserm, Inra UMR1220
Nathalie Vergnolle
Toulouse

Our team is the largest dedicated to the research on iron metabolism in France and its members are internationally recognized for their discovery of several of the key players in the regulation of hepcidin (i.e., BMP6, erythroferrone). Léon Kautz is an ERC-STG 2016 laureate.

Research Brief :

Our main objectives are: (i) to understand the molecular mechanisms necessary to adapt the quantity of iron absorbed through the duodenum to the iron needs for erythropoiesis; (ii) to find and validate new therapeutic targets to prevent iron overload associated with genetic hemochromatosis or beta-thalassemia and to divert iron from bacteria in infections with intra or extracellular pathogens.

• Methodologies Used :

Culture of mouse primary hepatocytes
Quantitative PCR and expression microarrays
Western blot
In situ hybridization
Immunohistochemistry
Production of recombinant proteins
Mouse microsurgery

Publications

Meynard D, Kautz L, Darnaud V, Canonne-Hergaux F, Coppin H, Roth MP. (2009). Lack of bone morphogenetic protein BMP6 induces massive iron overload., Nature Genetics. 41(), 478-81

Besson-Fournier C, Latour C, Kautz L, Bertrand J, Ganz T, Roth MP, Coppin H. (2012). Induction of activin B by inflammatory stimuli up-regulates expression of the iron-regulatory peptide hepcidin through Smad1/5/8 signaling., Blood. 120(), 431-9

Latour C, Kautz L, Besson-Fournier C, Island ML, Canonne-Hergaux F, Loréal O, Ganz T, Coppin H, Roth MP. (2014). Testosterone perturbs systemic iron balance through activation of EGFR signaling in the liver and repression of hepcidin., Hepatology. 59(), 683-94

Latour C, Besson-Fournier C, Meynard D, Silvestri L, Gourbeyre O, Aguilar-Martinez P, Schmidt PJ, Fleming MD, Roth MP, Coppin H. (2016). Differing impact of the deletion of hemochromatosis-associated molecules HFE and transferrin receptor-2 on the iron phenotype of mice lacking bone morphogenetic protein 6 or hemojuvelin., Hepatology. 63(), 126-37

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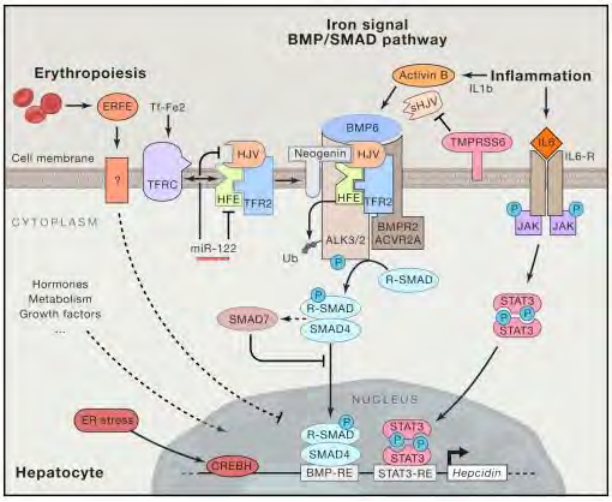
Hepcidin expression is regulated by iron signals, erythropoiesis, and inflammation



Our team is characterizing the mechanisms by which high iron stores (via BMP6, HJV, HFE, TFR2, and BMP/SMAD signaling), inflammation (via IL6, STAT3, and activin B) and ER stress (via TMPRSS6) activate hepcidin transcription. We are also investigating how ERFE, which is produced when erythropoietic activity is high, suppresses hepcidin.

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Key facts

Team

- Researchers : 5
- Technicians : 3
- Postdoc fellows : 1
- PhD Students : 2

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 1

International research links

- USA
- Italy
- Germany

Keywords

- Mitochondria
- Bioenergetics
- Metabolism
- Oxidative stress
- Cancer
- Fluorescence
- Metabolic fluxes
- Respirometry
- Biochemistry

Frédéric Bouillaud

Mitochondria, bioenergetics, metabolism and signaling

Université de Paris 05
(Université Rene Descartes)
CNRS UMR8104 Inserm U1016
Pierre-Olivier Couraud
Paris

Our general objective is to study the crosstalk between mitochondrial function, metabolism and diseases by deciphering the molecular mechanisms involved in mitochondrial adaptation to intrinsic and/or environmental insults.

Research Brief :

The aim of the team is to study how mitochondrial bioenergetics constitutes a determining factor for complex phenotypes. We address two different situations:
1) Bioenergetics is known to be the primary target of genetic defects, environmental or endogenous modifying factors; we then analyze how bioenergetic machinery (essentially mitochondria) is affected and subsequently both deleterious impact and potential compensatory responses at the cellular level.
2) Bioenergetics appears modified in pathological states (over-nutrition, obesity, diabetes, cancer?). Firstly, one should substantiate and characterise the qualitative and quantitative bioenergetic changes associated to the pathological state. Then the question of bioenergetic?s role is to be considered : does it constitute an adaptive response, an aggravating factor or could it be directly causative of the pathological state.
Our models are derived from human mitochondrial diseases or are based on modulation of specific genes (Ucp2, Cpt1, Sqr).

We consider that the transport of substrates across the mitochondrial is a critical control point and consider two systems the mitochondrial carrier UCP2 and the carnitine palmitoyl transferase 1 (CPT1. Our studies on sulfide bioenergetics illustrates the intrication between toxic, signaling and adaptive components.
Regular collaboration with teams needing to approach mitochondrial bioenergetics often provides additional models.

- **Methodologies Used :**

Respirometry (Oroboros and Seahorse)
Metabolic fluxes
ROS and membrane potential fluorescent probes
Molecular biology : recombinant DNA & immunodetection
Transgenic models

Publications

Esteves P, Pecqueur C, Ransy C, Esnous C, Lenoir V, Bouillaud F, Bulteau AL, Lombès A, Prip-Buus C, Ricquier D, Alves-Guerra MC (2014). Mitochondrial retrograde signaling mediated by UCP2 inhibits cancer cell proliferation and tumorigenesis., Cancer Res.. 74(4), 3971-82

Helmy N, Prip-Buus C, Vons C, Lenoir V, Abou-Hamdan A, Guedouari-Bounihi H, Lombès A, Bouillaud F (2014). Oxidation of hydrogen sulfide by human liver mitochondria., Nitric Oxide. 41(), 105-12

Hénique C, Mansouri A, Vavrova E, Lenoir V, Ferry A, Esnous C, Ramond E, Girard J, Bouillaud F, Prip-Buus C$, Cohen I (2015). Increasing mitochondrial muscle fatty acid oxidation induces skeletal muscle remodeling towards an oxidative phenotype., FASEB journal : official publication of the Federation of American Societies for Experimental Biology. 29(6), 2473-83

Vavrova E, Lenoir V, Alves-Guerra MC, Denis RG, Castel J, Esnous C, Dyck JRB, Luquet S, Metzger D, Bouillaud F, Prip-Buus C (2016). Muscle expression of a malonyl-CoA-insensitive carnitine palmitoyltransferase 1 protects mice against high-fat/high-sucrose diet-induced insulin resistance., Am J Physiol Endocrinol Metab.. 311(3), E649-60

Bouillaud F, Alves-Guerra MC, Ricquier D (2016). UCPs, at the interface between bioenergetics and metabolism, Biochim Biophys Acta - Molecular Cell Research. 1863(10), 2443-56

Lorenz C, Lesimple P, Bukowiecki R, Zink A, Inak G, Mlody B, Singh M, Semtner M, Mah N, Auré K, Leong M, Zabiegalov O, Lyras EM, Pfiffer V, Fauler B, Eichhorst J, Wiesner B, Huebner N, Priller J, Mielke T, Meierhofer D, Izsvák Z, Meier JC, Bouillaud F, Adjaye J, Schuelke M, Wanker EE, Lombès A, Prigione A. (2017). Human iPSC-Derived Neural Progenitors Are an Effective Drug Discovery Model for Neurological mtDNA Disorders., Cell Stem Cell. (),

Bouillaud Frédéric - frederic.bouillaud@inserm.fr

Key facts

Team

- Researchers : 9
- Technicians : 2
- Postdoc fellows : 2
- PhD Students : 3

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 0

International research links

- mexico
- germany

Keywords

- mitochondria, energy metabolism, mitochondrial dynamics, Crabtree, Warburg
- Oxygraphy, Sepctrophotometry, Fluorimetry

Anne Devin

Cell energy metabolism

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Unique combination of competencies in our team that studies cell energy metabolism and dynamics in isolated mitochondria, permeabilized cell and whole cells in a wide range of models : yeast, cultured cells, mouse. Our lab is at the forefront of research on mitochondrial energetics and dynamics.

Research Brief :

Cell energy metabolism includes energy conversion that leads to NADH reoxydation and ATP production. Two cellular pathways are involved in these processes: glycolysis and oxidative phosphorylation (mitochondria). Our laboratory is primarily involved in studying the control and regulation of oxidative phosphorylation during cell proliferation. Indeed the cellular needs for both ATP synthesis and NADH reoxydation are susceptible to huge variations with rapid kinetics and this requires tight adjustments from the cell. We thus study the mechanisms that allow such adjustments. This is achieved at three levels of integration: the cellular level, the isolated mitochondria level and the oxidative phosphorylation complexes level.
Furthermore, the influence of alterations of mitochondrial dynamics on energy metabolism is studied. Mitochondrial dysfunction is a common cause of disease in both children and adults. Within the cell mitochondria form a dynamic network as a result of balanced fusion and fission. Mammalian mitofusin 1 and mitofusin 2 belong to the GTPase family of proteins and are required for mitochondrial outer membrane fusion. The recent discovery of the role of MFN2 in maintaining the activity of the mevalonate pathway could help to address the great diversity of phenotypes related to the loss of MFN2 through a common metabolic origin.

• Methodologies Used :

The Laboratory possesses last generation Oroboros oxygraphs, Hitachi F7000 fluorimeter highly sensitive bioluminometer, spectrophotometers, thermal cycler....
The methodologies used range from molecular biology, western blotting, energy metabolism assessment, cell biology.

Publications

Diaz-Ruiz R, Rigoulet M, Devin A. (2011). The Warburg and Crabtree effects: On the origin of cancer cell energy metabolism and of yeast glucose repression., BBA bioenergetics. 1807(6), 568-76

Sauvanet C, Duvezin-Caubet S, Salin B, David C, Massoni-Laporte A, di Rago JP, Rojo M (2012). Mitochondrial DNA mutations provoke dominant inhibition of mitochondrial inner membrane fusion., PLOS one. 7(11), e49639

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Yoboue ED, Mougeolle A, Kaiser L, Averet N, Rigoulet M, Devin A. (2014). The role of mitochondrial biogenesis and ROS in the control of energy supply in proliferating cells., BBA bioenergetics. 1837(7), 1093--8

Mourier A, Motori E, Brandt T, Lagouge M, Atanassov I, Galinier A, Rappl G, Brodesser S, Hultenby K, Dieterich C, Larsson NG. (2015). Mitofusin 2 is required to maintain mitochondrial coenzyme Q levels., J Cell Biol.. 208(4), 429-42

Hammad N, Rosas-Lemus M, Uribe-Carvajal S, Rigoulet M, Devin A. (2016). The Crabtree and Warburg effects: Do metabolite-induced regulations participate in their induction?, BBA bioenergetics. 1857(8), 1139-46.

Devin Anne - Anne.Devin@ibgc.cnrs.fr - 0556999035 - http://ibgc.cnrs.fr/?page=equipe&eq=mec

Key facts

Team

- Researchers : 8
- Technicians : 8
- Postdoc fellows : 1
- PhD Students : 6

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 3

Keywords

- Small intestine
- Taste buds
- Estrogenic contaminants
- Lipid sensing
- Lipid-binding proteins
- Energy metabolism
- Chylomicrons
- Eating behavior
- Lipid signalling
- Obesity
- Integrative physiology

Biological Resources

- Transgenic mice
- Caco2, immortalized mouse taste bud cells

Naim Khan

Physiology of Nutrition & Toxicology (NUTox)

Université de Dijon
(Université de Bourgogne)
CHU Inserm U1231
Laurent Lagrost
Dijon

Exploration of the molecular and cellular mechanisms responsible for the chemodetection of dietary lipids along the oro-intestinal tract: impacts of estrogenic food contaminants and physiological or pathological consequences on the lipid metabolism, eating behavior and obesity risk

Research Brief :

The oro-intestinal tract plays a major role in the regulation of energy balance by controlling nutrient bioavailability and eating behavior. Recent data from our team and other investigations support the existence of a specific sensing system responsible for a real-time detection of lipids in ingested foods both in oral cavity and intestinal lumen. We have shown that the plasma membrane receptor CD36 plays a significant role in this detection as a lipid sensor involved in regulation of the spontaneous fat preference, digestive secretions and quality (size and number) of chylomicrons produced during the post-prandial period. Chemoreception of dietary lipids by the oro-intestinal tract appears to be complex since other lipid sensors candidates (e.g. GPR120) have recently been identified in these tissues. Interestingly, estrogenic contaminants of food contact materials might disturb this lipid sensing system by impairing the function of taste buds and small intestine. Our objective is to determine the respective role(s) of these lipid sensors and explore whether dysfunction in this oro-intestinal lipid sensing system leads to physio-pathological states increasing obesity risk and prevalence of associated plethora diseases. A better understanding of these mechanisms might leads to the development of novel therapies.

Methodologies Used :

Metabolic and behavioral phenotyping (indirect calorimetry, Echo MRI, lickometers)
Micro-surgery in the mouse
In situ isolated intestinal loop (intestinal lipid absorption)
Postprandial triglyceridemia, CD36 methylation,
Organ and cell cultures, genetic polymorphism
Molecular and cellular biology
Cell signalling
Clinical studies in humans

Publications

Dramane G, Abdoul-Azize S, Hichami A, Vögtle T, Akpona S, Chouabe C, Sadou H, Nieswandt B, Besnard P, Khan NA. (2012). STIM1 regulates calcium signaling in taste bud cells and preference for fat in mice., The Journal of clinical investigation. 22(2267), 2282

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Key facts

Team

- Researchers : 9
- Technicians : 3
- Postdoc fellows : 2
- PhD Students : 2

Translational approaches

- Patents : 1
- Clinical research grants : 2
- Industry partnerships : 3

Keywords

- Apolipoprotein
- Lipids
- Diabetes
- Obesity
- Adiponectin
- HDL
- Liver fat
- Kinetic study
- Stable isotopes

Biological Resources

- plasma samples from patients
- mice and rats obesitymodels
- cell cultures
- liver tissue explants
- fat tissue explants

Bruno Vergès

Pathophysiology of dyslipidemia (PADYS)

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Laurent Lagrost
Dijon

The work of our team is dedicated to the study of the pathophysiology of dyslipidemia in humans, mostly dyslipidemia associated with diabetes and insulin-resistance.

Research Brief :

For more than 10 years, our team has been working on the pathophysiology of dyslipidemia in humans, mostly dyslipidemia associated with diabetes and insulin-resistance. Our team includes scientists and also physicians who are working on both sides (clinic and research). This allows performing many translational studies "from bed to bench". Our main research activities within the field of "pathophysiology of dyslipidemia in humans" are built in 3 axes: 1) dysfunction of lipid metabolism in diabetes and insulin resistance (studied with in vivo human lipoprotein kinetic studies); 2) study of HDL in diabetes and insulin resistance; 3) involvement of the endocannabinoid system (ECS) in diabetes and insulin resistance.
During the 4 previous years we have shown:
- in type 2 diabetes, that hyperinsulinemia is not responsible for increased VLDL secretion and that rbp4 is an independent factor reducing VLDL catabolism
- that both catabolism and production of VLDL1-TG are independent determinants of HDL catabolism in the Metabolic Syndrome
- the importance of peripheral ECS on lipid and glucose metabolism and that ECS activation decreases fatty acid oxidation and increases adipose tissue lipolysis by altering the antilipolytic action of insulin
- that glycation and oxidation of HDL induces the loss of their vasorelaxant effect
- significant reduction in sphingosine-1-phosphate in HDLs from patients with type 1 diabetes or subjects with the Metabolic Syndrome,

• **Methodologies Used :**

In vivo kinetic studies in humans with stable isotopes
Ex vivo on vasorelaxetion using rabbit aorta rings
Animal studies
Cell culture
Hepatic tissue explants

Publications

Duvillard L, Florentin E, Pont F, Petit JM, Baillot-Rudoni S, Penfornis A, Vergès B. (2013). Chronic hyperinsulinemia does not increase the production rate of high-density lipoprotein apolipoprotein AI: evidence from a kinetic study in patients with insulinoma., Arterioscler Thromb Vasc Biol.. 33(10), 2460-5

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Alexandre Benani

Plasticity of brain feeding circuits

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Coupling state-of-the-art molecular analysis, histology and gene manipulation to investigate the neurobiological bases of feeding behaviour.

Key facts

Team

- Researchers : 3
- Technicians : 2
- Postdoc fellows : 0
- PhD Students : 2

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 0

Keywords

- Hypothalamus
- Obesity
- Food intake
- Neurobiology
- Vulnerability
- Feeding behaviour
- Molecular biology
- Histology
- Stereotaxy
- Tolerance tests

Biological Resources

- AgRP-cre mice
- POMC-cre mice
- RiboTag mice
- St8sia4 KO mice

Research Brief :

The team aims at a better understanding of the neurobiological basis of feeding behaviour.
First, we want to provide details about the structure of neuronal circuits that control food intake.
Second, we want to characterize the morphological plasticity of these networks (i.e. synaptic remodeling, modification of neuro-glial interactions, neurogenesis). We have shown that the structural plasticity of these networks is an essential element in the adaptive control of food intake. Indeed, reduced ability to structural plasticity in these networks could be a risk factor in obesity and related disorders.
Third, we want to characterize the influence of various internal and external factors on the feeding behaviour, such as the metabolic state (effect of overeating), the nutritional history (perinatal imprinting, food experience in adulthood), and pathological context (metabolic diseases, major depression, cachexia).

- **Methodologies Used :**

Use of standard and transgenic murine models.
Behavioral analysis (food intake, size and frequency of meals, satiety, preferences) and functional investigation (metabolic performance).
Molecular biology (gene regulation, chromatin remodeling, epigenetic).
Histology (neuroanatomy, neuronal tracing, cFos detection, immunohistochemistry).
Targeted intracranial manipulations (stereotactic injections of drugs and viral tools, shRNA-mediated silencing, pharmacogenetic).

Publications

Benani A, Hryhorczuk C, Gouazé A, Fioramonti X, Brenachot X, Guissard C, Krezymon A, Duparc T, Colom A, Nédélec E, Rigault C, Lemoine A, Gascuel J, Gerardy-Schahn R, Valet P, Knauf C, Lorsignol A, Pénicaud L (2012). Food intake adaptation to dietary fat involves PSA-dependent rewiring of the arcuate melanocortin system in mice., The Journal of neuroscience : the official journal of the Society for Neuroscience. 32(35), 11970-9

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Maurin AC, Benani A, Lorsignol A, Brenachot X, Parry L, Carraro V, Guissard C, Averous J, Jousse C, Bruhat A, Chaveroux C, B'chir W, Muranishi Y, Ron D, Pénicaud L, Fafournoux P (2014). Hypothalamic eIF2a signaling regulates food intake., Cell reports. 6(3), 438-44

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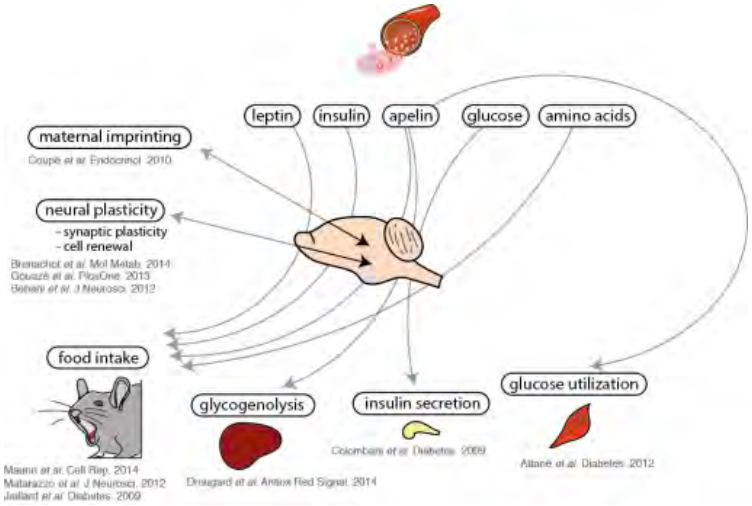
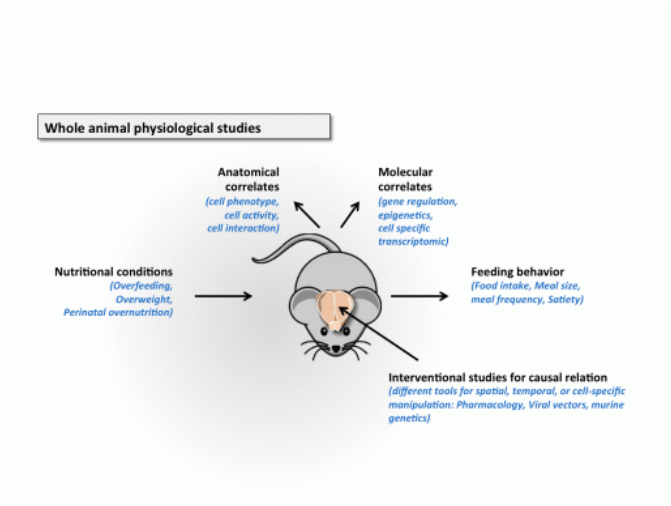
New insight into the mode of action of some metabolic cues



Models and skills



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Catherine Creuzot-Garcher
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Eye, Nutrition & Cell Signalling

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Through a translational research approach, our team aims to transform scientific discoveries arising from laboratory on the role of both endogenous and dietary lipids in the retina into clinical applications in the prevention of aging of the retina.

Key facts

Team

- Researchers : 7
- Technicians : 5
- Postdoc fellows : 0
- PhD Students : 3

Translational approaches

- Patents : 0
- Clinical research grants : 2
- Industry partnerships : 7

Keywords

- Prevention
- Nutrition
- Pathophysiology
- Aging
- Retina
- Lipid
- Chromatography
- Western-blotting
- qPCR
- Tonometry
- Angiography
- Funduscopy
- Electroretinography
- Flow cytometry

Biological Resources

- Human subjects and patients
- animal experiments in rodents
- retinal cell lines and primary cell cultures of retinal cells

Research Brief :

The demographic forecasts expect the elderly population to increase sharply in the next decades. Since eye diseases are the second most prevalent pathologies after the age of 65 years in Western countries, patients suffering from ocular pathologies are expected to represent a sensitive and growing socio-economic burden. Among those pathologies, age-related macular degeneration (AMD) and glaucoma are the leading cause of visual loss. Aging of the retina is characterized by specific clinical, functional and morphological features. Although lipids are key components of the retina, their roles are not fully defined. Lipids may both promote and prevent aging of the retina. Epidemiological studies have reported that dietary omega 3 fatty acids prevent from the development of AMD.
Through a translational research approach, our team aims to transform scientific discoveries arising from laboratory on the role of both endogenous and dietary lipids in the retina into clinical applications in the prevention of aging of the retina. Our projects aim to delineate whether lipids ? namely plasmalogens, cholesterol, and gangliodides ? and lipid metabolism participate in the functioning and dysregulations of the retina. The projects focus on 1) the mechanisms of lipid uptake to the retina, 2) the metabolic pathways that involve lipids as cell mediators in the retina, and 3) the links between pathologies and dysregulations of the lipid metabolism in the retina.

- **Methodologies Used :**

Patient evaluation
Animal and cell culture experiments
Electroretinography, funduscopy, angiography, tonometry
Biological evaluation (qPCR, Western-blotting, flow cytometry)
Chromatography (thin-layer, gas, high performance liquid), in tandem with mass spectrometry

Publications

Simon E, Bardet B, Grégoire S, Acar N, Bron AM, Creuzot-Garcher CP, Bretillon L (2011). Decreasing dietary linoleic acid promotes long chain omega-3 fatty acid incorporation into rat retina and modifies gene expression., Experimental Eye Research. 93(5), 628-35

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Alassane S, Binquet C, Cottet V, Fleck O, Acar N, Daniel S, Delcourt C, Bretillon L, Bron AM, Creuzot-Garcher C (2016). Relationships of Macular Pigment Optical Density With Plasma Lutein, Zeaxanthin, and Diet in an Elderly Population: The Montrachet Study., Investigative Ophthalmology & Visual Science. 57(3), 1160-7

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Charles-Henri Malbert

Ani-SCANs

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Aniscan is the sole facility that operates nuclear imaging in a large animal model either in the anaesthetised condition or in conscious animals. Furthermore, Aniscan get a recognised expertise in chronic vagal stimulation as a minimally invasive alternative to bariatric surgery.

Key facts

Team

- Researchers : 1
- Technicians : 1
- Postdoc fellows : 0
- PhD Students : 0

Translational approaches

- Patents : 0
- Clinical research grants : 1
- Industry partnerships : 4

International research links

- Center of research excellence in translating nutritional science in good health; University of Adelaide, Australia

Keywords

- Vagal stimulation
- Type 2 Diabetes
- Obesity
- Minimally invasive surgery
- Nuclear medicine
- Brain imaging

Biological Resources

- Miniature Pig

Research Brief :

We aimed to quantify the metabolic alterations induced by diet induced obesity with specific reference to brain-gut axis using nuclear imaging in a large animal model. To do so, we have developed several minimally invasive research tools to investigate receptor occupancy, glucose metabolism and blood flow in the miniature pig. We have build a unique three dimensional brain atlas of the pig together with additional digital ressources mandatory to use and quantify the information issued from the imaging machines. These resources were partially incorporated in AniMate and Pmod softwares. Concomitantly we have acquired a recognised expertise on the manipulation of the brain-gut axis through chronic stimulation of the abdominal vagus. We have demonstrated that, once applied bilaterally on the abdominal vagus, this stimulation was able to reduce food intake and to restore insulin sensitivity in a model of diet induced morbid obesity. This occurs simultaneously at the muscle, liver and brain level. Furthermore, we showed that vagal stimulation was associated with improved limbic connectivity - a feature altered by acquired obesity. Finally, we developed a new stimulating scheme dedicated to the abdominal vagus nerve capable of activation of C type neurons within the limitations of an implantable neurostimulator. This scheme was able to activate the dorsal vagal complex and the majority of its efferents areas with a striking similarity to the brain activation observed postprandially

- **Methodologies Used :**

PET imaging using 18F or 68Ga derivatives. Dynamic PET imaging with in line and off line arterial radioactivity measurements.
Brain SPECT imaging using Tc99m and 123 Iodine derivatives
Dynamic planar abdominal imaging in conscious pigs for measurement of solids and liquids gastric emptying
CT based body composition
Image guided brain surgery including in situ neuronal recordings
Minimally invasive ultrasound guided surgery for arterial/venous catheter placements and biopsies
Minimally invasive placement of electrodes on abdominal vagal trunks using laparoscopic surgery
Indirect calorimetry in anaesthetised animals
Evaluation of microstructure of the meal and meal preferences using robotic feeders

Publications

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Val-Laillet D, Aarts E, Weber B, Ferrari M, Quaresima V, Stoeckel LE, Alonso-Alonso M, Audette M, Malbert CH, Stice E (2015). Neuroimaging and neuromodulation approaches to study eating behavior and prevent and treat eating disorders and obesity, Neuroimage Clin. 24(8), 1-31

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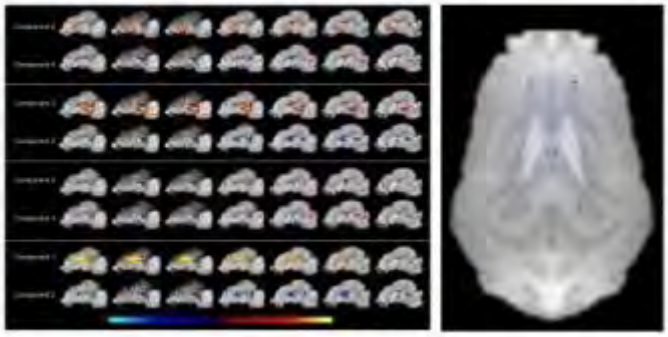
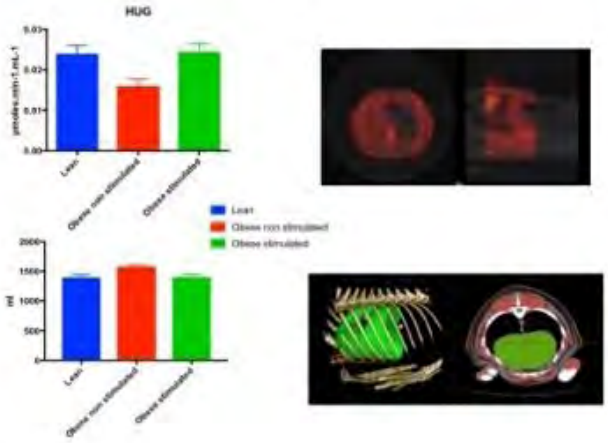
Multimodal analysis of the brain activity after vagal stimulation



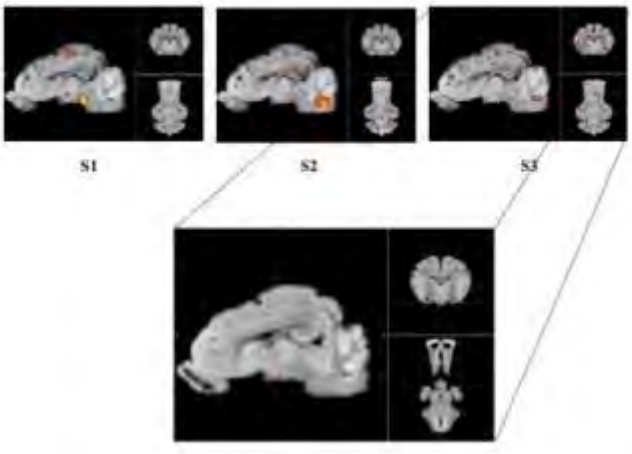
Multimodal analysis of FDG (glucose metabolism) and DATScan (DAT receptor binding) obtained in vagal stimulated versus control obese miniature pigs. Left image - Independent component analysis aims to identify independent components in each image modality as well as the relationships of these independent components across image modalities. Right - We applied a group ICA algorithm to define coherent network components. The width of each line indicates the strength of the relationship.

Hepatic glucose uptake after vagal stimulation



Changes in hepatic glucose uptake (dynamic PET FDG imaging) and hepatic volume (CT imaging) in lean, obese and obese animals with chronic vagal stimulation during 12 weeks. Note the restoration of the insulin sensitivity (expressed as MRglu) obtained by vagal stimulation. Hepatic glucose uptake was calculated in insulin stimulation condition obtained by insulin clamp. This allow to extract the whole body insulin sensitivity together with the hepatic glucose production and uptake.

Effect of various vagal stimulation patterns on brain activity



Statistical parameter mapping (SPM) of the brain FDG uptake obtained in vagally stimulated versus control animals. SPM analysis was performed on pixelwise MRGlu calculated images to take into account absolute variation in the overall glucose uptake. Three modalities of vagal stimulation were compared to control (S1, S2 and S3). S2 and S3 were specifically designed to activate C neurons. Only S3 pattern was able to increase the metabolism of the dorsal vagal and hypothalamic complexes

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Oncogenesis Stress Signaling

Eric Chevet

Protein Homeostasis and Cancer (PROSAC)

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Key facts

Team

- Researchers : 5
- Technicians : 3
- Postdoc fellows : 1
- PhD Students : 8

Translational approaches

- Patents : 3
- Clinical research grants : 0
- Industry partnerships : 2

International research links

- Ireland
- Chile
- Canada

Keywords

- endoplasmic reticulum
- stress
- protein misfolding
- cancer
- screening
- cell and molecular biology
- integrated approaches

Integrated study of Endoplasmic reticulum functions in health and disease.

Research Brief :

Our team focuses on the study of Endoplasmic Reticulum (ER) functions in health and disease. In particular we are interested in better understanding two major molecular machines of the ER, namely the stress signalling machinery and the quality control machinery. The first research axis developed in the laboratory aims at characterizing ER stress signalling actors important for tumour development. Indeed in solid tumours, cells are subjected to major environmental challenges that condition their growth and fate. Under those circumstances, protein folding in the ER is affected and ER stress signalling is activated (the Unfolded Protein Response pathway). Our studies focus mainly on IRE1, the most conserved ER stress signal transducer, in various cancers including hepatocellular carcinoma and glioblastoma. The second research axis developed in the laboratory aims at characterizing novel component of the ER quality control whose expression is regulated upon IRE1 activation. We focus on proteins which specifically participate to the control of misfolded proteins secretion in the liver. Our third research axis focuses on the identification of IRE1 activity modulators through automated screening using the AlphaScreen® technology. These approach provide an integrated framework to better characterize and perturb ER biology in health and disease.

Methodologies Used :

Cell and molecular biology
In vitro and cell-based assays
Automated analases, alphascreen

Publications

Negroni L, Taouji S, Arma D, Pallares-Lupon N, Leong K, Beausang LA, Latterich M, Bossé R, Balabaud C, Schmitter JM, Bioulac-Sage P, Zucman-Rossi J, Rosenbaum J, Chevet E (2014). Integrative quantitative proteomics unveils proteostasis imbalance in human hepatocellular carcinoma developed on nonfibrotic livers., Mol Cell Proteomics.. (),

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Olivier Loréal

Control of Iron Metabolism and Iron Associated Diseases

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Key facts

Team

- Researchers : 20
- Technicians : 5
- Postdoc fellows : 2
- PhD Students : 7

Translational approaches

- Patents : 3
- Clinical research grants : 5
- Industry partnerships : 1

Keywords

- iron metabolism
- hepcidin
- hemochromatosis
- iron metabolism disease
- Microbiology
- metals
- microbiota
- parodontitis
- hepatocellular carcinoma
- osteoporosis
- cell biology
- molecular biology
- animal models
- in vitro models
- bio-clinical studies
- microbiology
- ICP-MS
- microbiota

Biological Resources

- Database on Rare genetic iron overload diseases with CHU (National Reference Center).
- Participation in the hepatology part of the Biological Ressource Center of Rennes.
- In vitro hepatic and digestive models
- Iron overload animal models and stored samples
- Iron overload animal models and correspponding stored samples

Integration between basic and bio-clinical studies in order to improve knowledge on iron metabolism physiology and diseases, as well as mechanisms involved in their complications.

Research Brief :

Disturbances in iron homeostasis, including iron excess, affect well-being and life expectancy. However, huge differences exist in the phenotype of genetic iron overload disease. Identifying the causes of this variability is a major challenge for the development of methods that would control iron metabolism diseases. In order to get a better knowledge of those mechanisms, with the perspective of identifying targets for the control of iron-related diseases, we are characterizing new factors that may control iron level in plasma ?a hub for iron metabolism-, including :
i) the impact of expression and/or activities of proteins involved in the control of iron concentration in plasma, such as hepcidin, ferroportin and ceruloplasmin, their links with other metals and the impact of chelators;
ii) the relationships between microbiota and iron metabolism to determine how digestive microbiota may modulate iron metabolism, and whether iron overload disease has an impact on bacteria virulence, by studying oral microbiota that is easily accessible and will permit to study the relationships between iron excess, bacteria and lesions by focusing on periodontal diseases.
We are performing an integrative approach with original models and platforms devoted to metal quantification and metabolism in links with physicians (hepatologists, rheumatologists, odontologists), the clinical Investigation center and the National Reference Center for Rare Genetic Iron Overload Diseases.

- **Methodologies Used :**

- Human and mouse hepatocytes cultures
- wild type and knock-out mice and rat models exposed or not to stimuli known to impact cellular or systemic iron metabolism.
- Gene expression studies.
- Functional studies allowing analysis of gene function and the impact of mutations.
- Bioclinical studies in patients through clinical, biochemical and genetic parameters.
- Use of databases for correlations between phenotype and genotype.
- Biochemical tools giving access tmetabolic studies (stable isotopes and ICP/MS.
- Biofilms models
- Microbiota studies

Publications

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The CIMIAD Team

The CIMIAD team characterizes the iron metabolism with special regards on the place of hepcidin on the iron biodistribution within the body and its relationships with other metals and microbiota, as well as the impact of iron excess on liver, bones and oral health during iron overload diseases.

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David Jacobi

Diurnal mitochondrial rhythms and metabolic diseases

Université de Nantes
Inserm UMR1087 CNRS UMR6291
Richard Redon
Nantes

A unique approach combining circadian and mitochondrial biology

Key facts

Team

- Researchers : 1
- Technicians : 0
- Postdoc fellows : 1
- PhD Students : 1

Translational approaches

- Patents : 0
- Clinical research grants : 1
- Industry partnerships : 0

Keywords

- Metabolic diseases
- Mitochondrial dynamics
- Circadian rhythms
- Mouse metabolic phenotyping
- Mouse models of overnutrition

Research Brief :

Over 50% of adults in European Union (EU) countries are overweight and therefore at risk of developing metabolic diseases such as type 2 diabetes or non-alcoholic steatohepatitis. The characteristics of modern lifestyle, such as excessive consumption of food and sedentary behaviour, contribute to this situation. But we also see changes in feeding and sleep / wake rhythms that contribute to overweight and metabolic complications. However, the mechanisms linking irregular lifestyles to overweight and metabolic complications are poorly understood.

The rationale for our research program is based on the following observations:
1. The liver plays a central role in adapting to physiological alternation between fasting / fed state.
2. Liver metabolism is regulated by an internal clock.
3. The control of mitochondria by the hepatic clock is essential to the normal functioning of the liver (Jacobi et al., Cell Metabolism 2015).

We therefore use in vitro and in vivo approaches to study hepatocyte metabolism. Genetic, pharmacological, and metabolic approaches are used to delineate the molecular mechanisms by which overnutrition and loss of circadian synchrony disturbs mitochondrial rhythms. Then, we establish how these alterations trigger metabolic diseases.
We take advantage of the unique environment of the Institut du Thorax and its research unit to demonstrate the relevance of our results in clinical populations of obese patients.

Methodologies Used :

Clock deficient and time-restricted fed mice
Synchronized hepatocytes
Super resolution microscopy
Mitochondrial lipidomics
Resonance paramagnetic spectrometry

Publications

Jacobi D, Liu S, Burkewitz K, Kory N, Knudsen NH, Alexander RK, Unluturk U, Li X, Kong X, Hyde AL, Gangl MR, Mair WB, Lee CH (2015). Hepatic Bmal1 Regulates Rhythmic Mitochondrial Dynamics and Promotes Metabolic Fitness, Cell Metab. 22(4), 709-20

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Jacobi David - David.Jacobi@univ-nantes.fr -

Ramaroson Andriantsitohaina

Oxidative stress and metabolic diseases

Université d' Angers
Inserm UMR1063
Ramaroson Andriantsitohaina
Angers

Key facts

Team

- Researchers : 12
- Technicians : 5
- Postdoc fellows : 2
- PhD Students : 7

Translational approaches

- Patents : 3
- Clinical research grants : 3
- Industry partnerships : 0

Keywords

- oxidative stress
- extracellular vesicles
- metabolic diseases
- polyphenols
- Flow cytometry
- confocal microscopy
- oxygraphy
- myography
- molecular biology

Biological Resources

- Cohorts

Translational research depicting the role of oxidative stress in metabolic diseases with special interest in extracellular vesicles and in the potential therapeutic of polyphenols to correct the deleterious effects related with oxidative stress.

Research Brief :

Extracellular vesicles (EVs) and metabolic dysfunctions: interrelationship between metabolic syndrome (MetS) and obstructive sleep apnea (OSA)
The main goal is to predict MetS development and its interrelationship and penetration with OSA with into overt disease as well as define new therapeutic opportunities from the delivery of "specific" vesicle subsets. Thus, the focal point of the project is EVs bringing novelty, and establishing possibly a selling point in view of concepts uniqueness. For disease outcome, the focus will be of common downstream consequences of MetS and OSA such as increased cardiovascular morbidity including peripheral vascular diseases and coronary artery disease.

Therapeutic strategies to fight against metabolic dysfunctions: EVs and nutritional approaches.
EVs will be engineered to over-express different therapeutic players (proteins, mRNA or miRNA) by driving the synthesis of the relevant EV-producing cells. A goal will be the selection of specific EV subsets to assess their therapeutic potential in proof-of-concept analyses.
We will investigate an optimization of the impact of nutrients from carrot, apple and red wine polyphenol compounds against metabolic diseases. This will be addressed in an integrative manner with regard to the impact of plant genetic variability, culture conditions and conservations on different cells of interest (vascular, adipocytes and hepatocytes) and in experimental models of insulin resistance and obesity.

- **Methodologies Used :**

? In vivo (echography, laser doppler, telemetry) and in vitro (myography, arteriography, langerdorff) approaches: animal models (pharmacology, knock out).
? Cell culture (primary cells and cell lines) and biology (flow cytometry, confocal microscopy, patch clamp, oxygraphy). Molecular biology (quantitative PCR, Western blot, gene silencing)
? Clinical studies (epidemiology, pharmacology, genetics).

Publications

Chalopin M, Soleti R, Benameur T, Tesse A, Faure S, Martinez MC, Andriantsitohaina R (2014). Red wine polyphenol compounds favor neovascularisation through estrogen receptor ?-independent mechanism in mice, PLoS ONE. 9(), e110080

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Gagnadoux F, Pépin JL, Vielle B, Bironneau V, Chouet-Girard F, Launois S, Meslier N, Meurice JC, Nguyen XL, Paris A, Priou P, Tamisier R, Trzepizur W, Goupil F, Fleury B. (2017). Impact of mandibular advancement therapy on endothelial function in severe obstructive sleep apnea., Am J Respir Crit Care Med. (),

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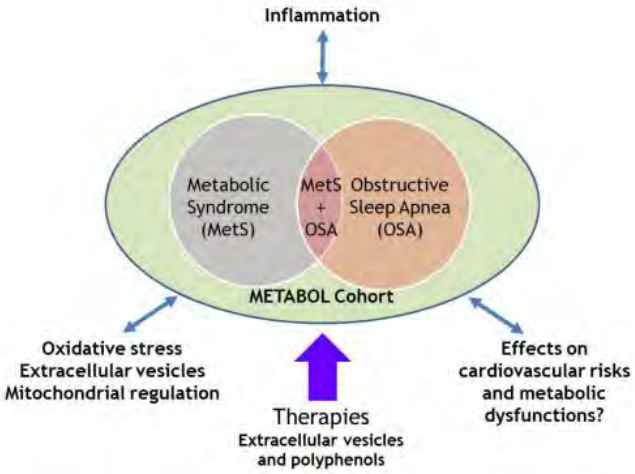
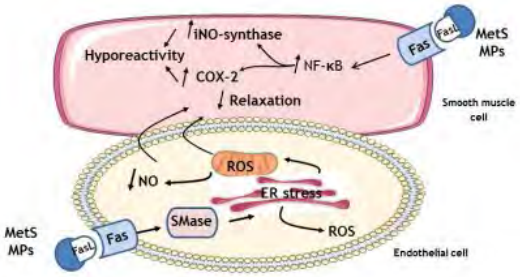
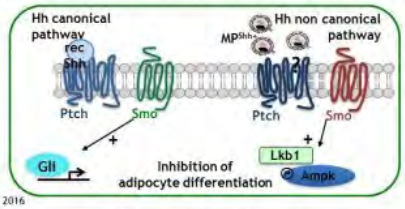


Microparticles: Biomarkers and vectors of inflammation
Metabolic syndrome

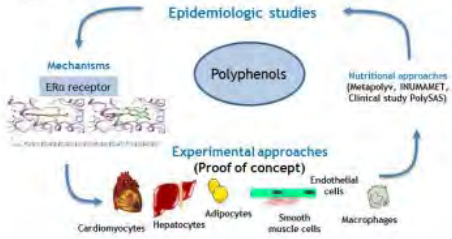


Agouni *et al.*, Am J Pathol 2008; PLoS One 2011
Safiedeen *et al.*, Antioxid Redox Signal 2017

Therapeutic strategies of metabolic diseases: EVs and Polyphenols



Fleury *et al.*, Sci Reports 2016



Andriantsitohaina Ramaroson - ramaroson.andriantsitohaina@un iv-angers.fr - sopam.univ-angers.fr

Key facts

Team

- Researchers : 23
- Technicians : 9
- Postdoc fellows : 5
- PhD Students : 11

Translational approaches

- Patents : 3
- Clinical research grants : 4
- Industry partnerships : 6

Keywords

- polyunsaturated fatty acids
- diet
- prostate cancer
- Cholesterol
- Alkyl-Ether-Lipids
- tumor chemosensitization
- ion channels
- lipidome
- membrane transporters
- invasiveness
- cell migration
- Calcium
- Breast cancer
- mitochondrial bioenergetics.
- fluorescence microscopy.
- Lipid
- Electrophysiology
- clinical trial
- calorimetric chambers
- invasion
- Rodents models of breast cancer
- cell cultures (proliferation
- migration

Biological Resources

- Metastatic Breast Cancer Patients
- Breast Cancer cell cultures
- Prostate Cancer cell cultures
- Rodent models of mammary tumor
- Biobank of human adipose tissues
- Biobank of human prostate tumor tissues

Christophe Vandier

Nutrition, Growth and Cancer

Université de Tours
(Université Francois Rabelais)
Inserm UMR 1069 CHU UMR 1069
Christophe Vandier
Tours

Our objectives are to establish a rationale for implementing clinical trials using specific lipid to increase anticancer treatment efficacy, to prevent metastasis, to limit therapeutic relapse in chronic forms of prostate/breast cancers, to fight cancer cachexia and allow better tolerance to drugs.

Research Brief :

The research unit has a long-standing expertise in performing research at the interface between nutrition and cancer, and has received international recognition in this field. The team was the first to link diet-related changes in the breast-associated adipose tissue (lipidome) in relation to breast cancer development and metastasis. This finding is highly consistent with the hypothesis that the western diet plays a pivotal role in the development and the progression of several high incidence and mortality-inducing tumor types, including breast and prostate cancers. UMR1069 has also described the potential benefits of the clinical use of lipid nutrients in order to increase anticancer treatment efficiency. Cancer-induced cachexia, a progressive alteration in the nutritional status of patients that drastically affects their survival, is another association between cancer and nutrition being investigated. Specific dietary and pharmacological lipid interventions may have important beneficial effects and clinical applications.
Our scientific project aims at investigating the cellular mechanisms of action of lipids (ether-lipids, cardiolipins, polyunsaturated fatty acids) to regulate cancer cachexia and tumor progression (bed to bench side). The objective is to facilitate the transfer of of such fundamental knowledge to patients developing chemo-or hormono-resistant cancers and/or metastases and/or cancer-induced cachexia (bench to bedside).

- **Methodologies Used :**

Randomized clinical trial in cancer patients, Analysis of energy metabolism in humans and rodents, Mouse and rat models of breast tumors and metastases, Epithelial cell cultures (proliferation, migration, invasion), Organotypic cultures, Electrophysiology of cancer cells (automated platform in development)and in tissues, Calcium homeostasis, Lipid biochemistry (chromatography, spectrometry) and chemical synthesis, Bioenergetics analysis of mitochondrial functions, Molecular and cellular tools (cloning, siRNA, PCR and Western blotting, lentivirus transfection), Bright field, phase contrast and fluorescence microscopy and Macroscopy. Hypoxia chamber.

Publications

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Figiel S, Pinault M, Domingo I, Guimaraes C, Guibon R, Besson P, Tavernier E, Blanchet P, Multigner L, Bruyère F, Haillot O, Mathieu R, Vincendeau S, Rioux-Leclercq N, Lebdai S, Azzouzi AR, Perrouin-Verbe MA, Fournier G, Doucet L, Rigaud J, Renaudin K, Mahéo K, Fromont G. (2018). Fatty acid profile in peri-prostatic adipose tissue and prostate cancer aggressiveness in African-Caribbean and Caucasian patients., Eur J Cancer.. 91(91), 107-1115

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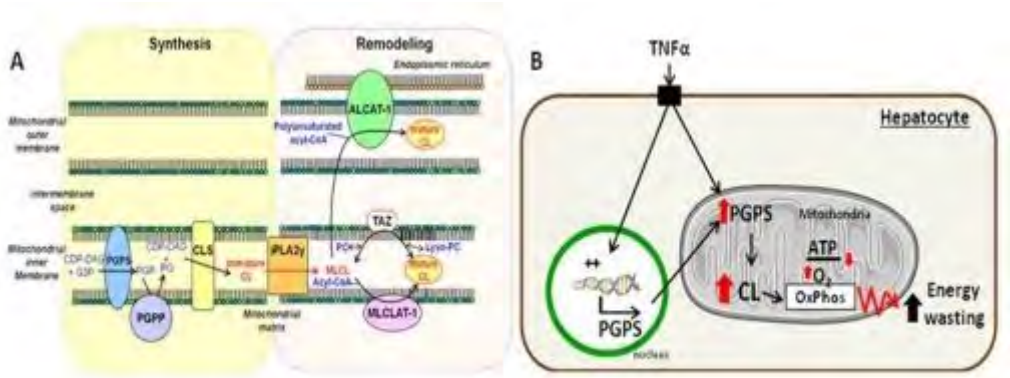
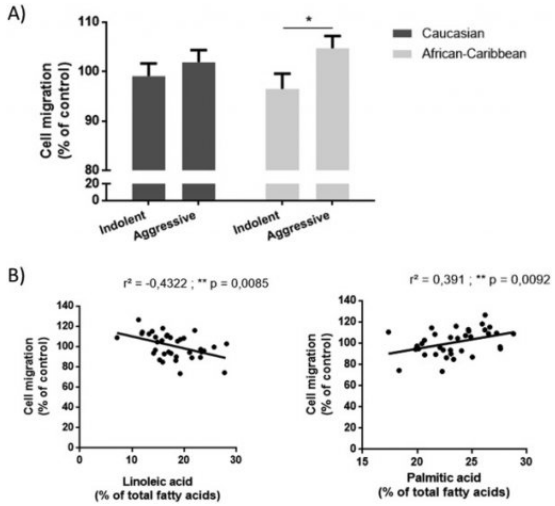
Cardiolipin de novo synthesis and remodeling on the matrix side of the inner mitochondrial membrane



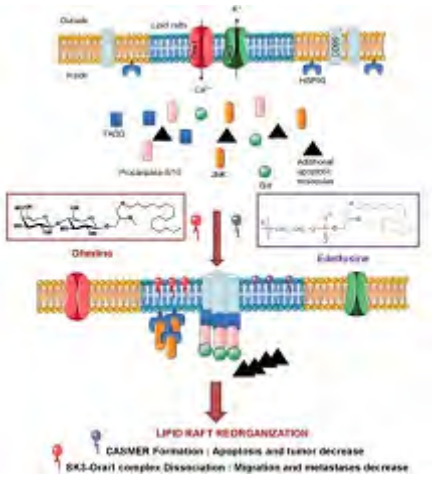
CL metabolism is dependent on biosynthesis and remodeling of the fatty acid composition. Liver mitochondria from cachectic animals display lower oxidative phosphorylation efficiency compared to pair-fed animals, due to increased energy wasting processes. There is a positive correlation between CL content and energy wasting intensity. PGPS enzyme was upregulated in liver mitochondria from cachectic rats. PGPS expression was upregulated by TNFa, associated with a specific increase in CL content.

Effects of peri-prostatic adipose tissue (PPAT) on the migration of prostate cancer cells



Effects of PPAT on the migration of prostate cancer cells. Fatty acids from PPAT were extracted from Caucasian (n = 36) and African?Caribbean (n = 36) patients. A) Histograms showing cell migration with fatty acids from Caucasian and African?Caribbean PPAT for 24 h. B) Correlation between the migration of prostate cancer cells and the level of linoleic acid and palmitic acid in African?Caribbean patients.

Proposed mechanism of action of Alkyl-Ether-Lipids (AEL) in tumor cells



SK3 and Orai1 channels are embedded within lipid rafts and form a complex regulating cancer cell migration and metastasis development. The supramolecular entity CASMER is not formed in this condition and cells are resistant to apoptosis. The reorganization of lipid raft induced by AEL allows Orai1-SK3 to move away from lipid rafts and abolishes SK3-dependent constitutive calcium entry. Edelfosine recruits a number of apoptotic signaling molecules in lipid rafts to generate the the CASMER.

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Key facts

Team

• Researchers : 6
• Technicians : 5
• Postdoc fellows : 4
• PhD Students : 2

Translational approaches

• Patents : 2
• Clinical research grants : 2
• Industry partnerships : 2

International research links

• European Union, United States,
Canada, Brazil

Keywords

• Vascular function and endothelium
• Polyphenols
• Oxylipins and lipid mediators
• Biomarkers exposure and health
• Dietary plant food bioactives
• Targeted lipidomics
• Food Metabolome
• Nutrigenomics
• Clinical trials

Biological Resources

• Primary human endothelial and macrophages and monocytes cell
lines
• Animal experiments in rodents and minipigs
• Healthy subjects and patients

Christine Morand

Nutrivasc - Diet, Plant food bioactives & Vascular Health

Université Clermont Auvergne
INRA UMR1019
André Mazur
Clermont Ferrand

Through a translational approach, our research aim to provide scientific evidence of the role of dietary plant food bioactive compounds, mainly polyphenols, in the prevention of vascular dysfunction and to produce knowledge on the cellular and molecular mechanisms involved.

Research Brief :

Maintaining vascular function is essential in preserving health and healthy aging. Early vascular dysfunction is associated with initiation of atherosclerosis, CVD development and contributes to the occurrence of type 2-diabetes and cognitive decline. Therefore, it is of great importance to identify innovative and scientifically sound dietary strategies to prevent vascular dysfunctions. Evidence from large prospective cohort studies have pointed out that dietary bioactive plant compounds contribute to the cardiovascular protective effects of diets rich in plant foods. However, the actual impact of most of these compounds in human and their mechanisms of action have not yet been fully established. In this context, using a translational approach and combining classical and "omics" methodologies, the research of the NutriVasc team focuses on understanding the role of plant food bioactives in the prevention of vascular dysfunctions, with as major objectives:
1. Provide clinical evidence of the role of bioactive compounds (polyphenols, phytoprostans) in the prevention or delay of vascular dysfunction and unravel the complexity of the underlying cellular and molecular mechanisms of action,
2. Characterize the complexity of the individual exposure to plant bioactive metabolites by the Food Metabolome approach,
3. Identify the main determinants of inter-individual variation in the response to the consumption of plant food bioactives (bioavailability and vascular protective effects).

• **Methodologies Used :**

Randomized controlled trials in humans / Animal models of atherosclerosis and cell culture (endothelial cells, monocytes, macrophages) / Non-invasive assessment of vascular function (endothelial function in micro and macrocirculation, arterial stiffness) / Biological evaluation (biochemical analysis, immuno-histochemistry, histology, flow cytometry) / Molecular and cellular analysis: gene expression (qPCR, transcriptomics), protein expression (Western blotting, proteomics), chemotaxis, monocyte adhesion, transendothelial migration, macrophage polarization / Targeted lipidomics based on LC-MS/MS mass spectrometry to characterize lipid mediators / Metabolomics based on high resolution mass spectrometry to characterize the food metabolome

Publications

Chanet A, Milenkovic D, Deval C, Potier M, Constans J, Mazur A, Bennetau-Pelissero C, Morand C and Bérard A (2012). Naringin, the major grapefruit flavonoid, specially affects atherosclerosis development in diet-induced hypercholesterolemia in mice, Journal of Nutritional Biochemistry. 23(5), 469-477

Rothwell JA, Fillâtre Y, Martin JF, Lyan B, Pujos-Guillot E, Fezeu L, Hercberg S, Comte B, Galan P, Touvier M and Manach C (2014). New biomarkers of coffee consumption identified by the non-targeted metabolomic profiling of cohort study subjects, PloS ONE. 9(4), e93474

Habauzit V, Verny M, Milenkovic D, Barber-Chamoux N, Mazur A, Dubray C and Morand C (2015). Flavanones protect from arterial stiffness in postmenopausal women consuming grapefruit juice for 6-months: A randomized controlled crossover trial, American Journal of Clinical Nutrition. 102(1), 66-74

Manach C, Milenkovic D, Van de Wiele T, Rodriguez-Mateos A, de Roos B, Garcia-Conesa MT, Landberg R, Gibney ER, Heinonen M, Tomas-Barberan F, Morand C (2016). Addressing the inter-individual variation in response to consumption of plant food bioactives: Towards a better understanding of their role in healthy aging and cardiometabolic risk reduction, Molecular Nutrition & Food Research. (),

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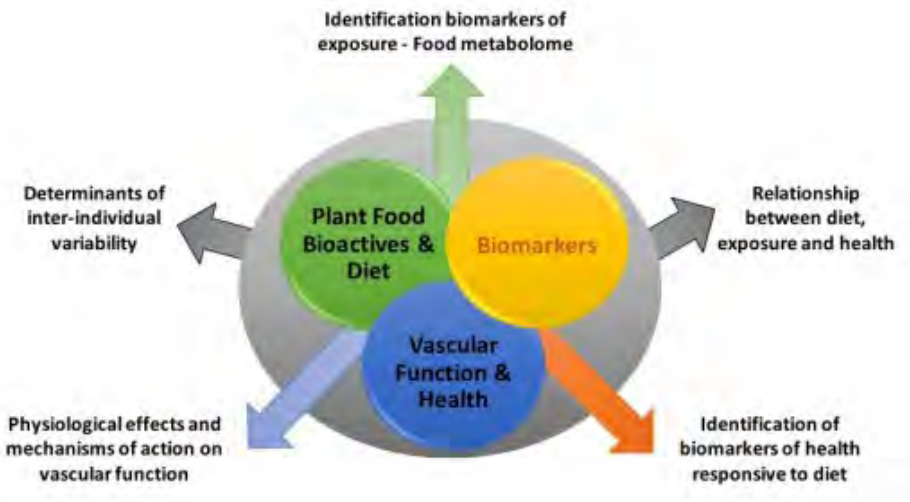
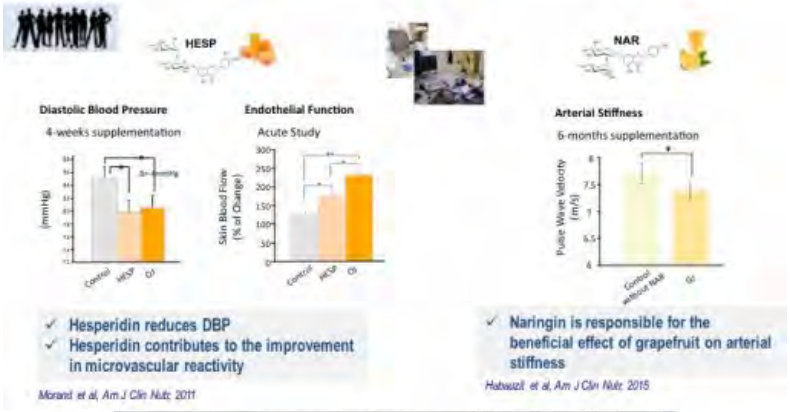
Outlines of the research developed in the NutriVasc Team

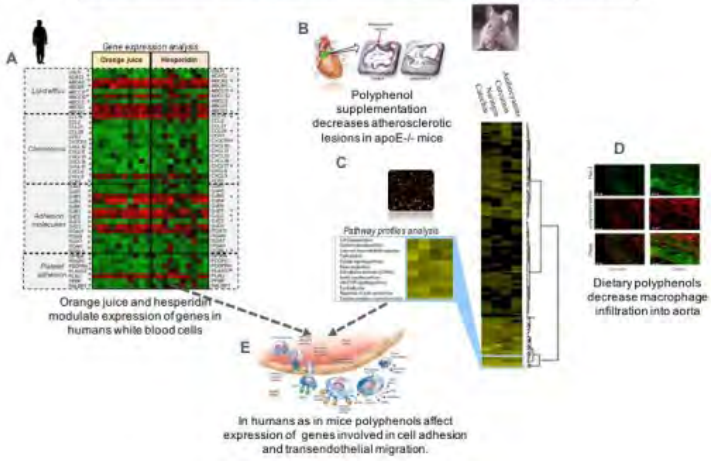


Exemples of key findings

First clinical evidence of the role of flavanones in the beneficial effect induced by citrus foods consumption on vascular function



Identification of cellular and molecular targets of dietary polyphenols



Morand Christine - christine.morand@inra.fr - +33473624084 - https://www6.clermont.inra.fr/unh/Equipes-de-Recherche/NutriVasc

Unité de Nutrition Humaine

Pierre Fafournoux

Protein Metabolism Nutrition and Aging

Université d'Auvergne
Clermont-Ferrand 1
INRA UMR1019
André Mazure
Clermont-Ferrand

Key facts

Team

- Researchers : 18
- Technicians : 10
- Postdoc fellows : 5
- PhD Students : 14

Translational approaches

- Patents : 2
- Clinical research grants : 0
- Industry partnerships : 0

International research links

- Italy, Nederland, Canada, UK, Australia, USA

Keywords

- Nutrition
- Amino Acids
- Protein
- metabolism
- eIF2a signaling
- Molecular Physiology
- Nutrients fluxes
- transgenic mice
- gene expression
- nutritional intervention

Biological Resources

- Human studies on healthy volunteers
- Animal models (transgenic mice, rat, mini pigs?)
- Cell lines
- Access to human cohorts and human biopsies

Our team has a strong expertise in studying the mechanisms responsible for the maintenance of protein/amino acid homeostasis during physiological and catabolic states.

Research Brief :

Numerous diseases (cancer, sepsis,) and aging are frequently associated with a dysregulation of amino acid and protein homeostasis. The main consequence is a catabolic state that strongly contributes to the deterioration of patients health and compromises treatments. The main objectives of the team are to understand the mechanisms involved in maintaining protein/amino-acid homeostasis. The endpoint is to develop pharmacological and nutritional strategies to prevent and/or attenuate protein/amino acid homeostasis dysregulations.
Our work focuses on three complementary research themes studying different aspects of the regulation of the metabolism of amino acids and proteins during several physiological and pathological situations (perinatal nutrition, muscle wasting, food intake disorders, aging,):
-Characterization of the molecular mechanisms involved in adaptation to variations in amino acid availability.
-Regulation of tissue protein metabolism: protein synthesis and proteolysis (ubiquitin-proteasome system, autophagy).
-Regulation of inter-organ relationships for the use of amino acids.

• Methodologies Used :

Cellular and molecular biology
Gene knock-down and over-expression in vivo and in vitro (electroporation, viral vectors,)
Proteolysis and protein synthesis determination
Gene expression measurement (qPCR, polysome analysis)
Metabolomics / proteomics
In situ hybridization and immunohistochemistry
Recombinant protein production and purification
Biomolecular interaction studies (Surface Plasmon Resonance, Y3H and Y2H, etc.) Nutritional interventions in humans and in animal models
Food digestion and digestibility in cannulated animal models
In vivo nutrients fluxes evaluation
Access to human cohorts

Publications

Polge C, Heng AE, Jarzaguet M, Ventadour S, Claustre A, Combaret L, Béchet D, Matondo M, Uttenweiler-Joseph S, Monsarrat B, Attaix D, Taillandier D (2011). Muscle actin is polyubiquitinylated in vitro and in vivo and targeted for breakdown by the E3 ligase MuRF1, Faseb J. 25(), 3790

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Maurin AC, Benani A, Lorsignol A, Brenachot X, Parry L, Carraro V, Guissard C, Averous J, Jousse C, Bruhat A, Chaveroux C, B'chir W, Muranishi Y, Ron D, Pénicaud L, Fafournoux P (2014). Hypothalamic eIF2a signaling regulates food intake, Cell Reports. 6(3), 438

C. Chaveroux, V. Carraro, L. Canaple, J. Averous, A.-C. Maurin, C. Jousse, Y. Muranishi, L. Parry, F. Mesclon, E. Gatti, J. Mallet, P. Ravassard, P. Pierre, P. Fafournoux, and A. Bruhat (2015). In vivo imaging of the spatiotemporal activity of the eIF2a-ATF4 signaling pathway: Insights into stress and related disorders, Science Signaling. 8(374), rs5

Deval C, Capel F, Laillet B, Polge C, Béchet D, Taillandier D, Attaix D, Combaret L. (2016). Docosahexaenoic acid-supplementation prior to fasting prevents muscle atrophy in mice, J Cachexia Sarcopenia Muscle. 7(), 587

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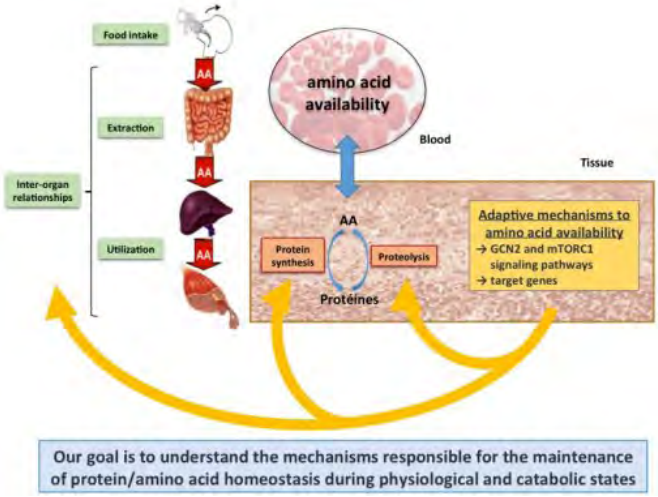
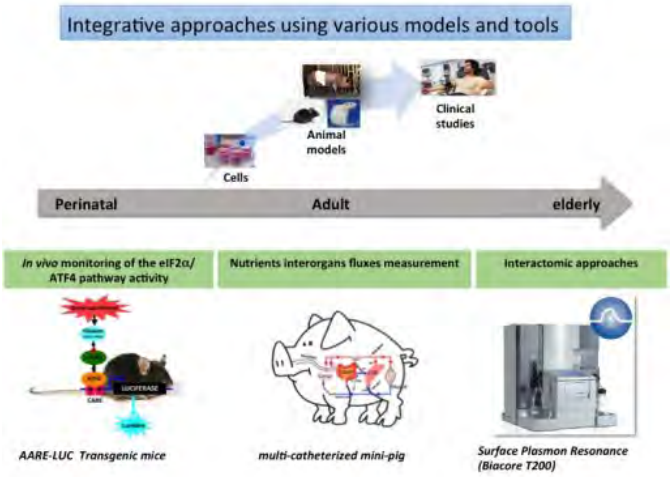
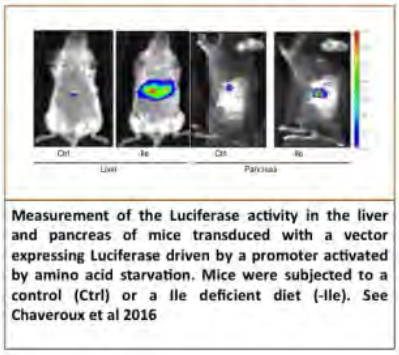
Protein/Amino Acid homeostasis



Integrative approaches using various models and tools



Regulating the expression of therapeutic transgenes by controlled intake of dietary essential AA



Measurement of the Luciferase activity in the liver and pancreas of mice transduced with a vector expressing Luciferase driven by a promoter activated by amino acid starvation. Mice were subjected to a control (Ctrl) or a Ile deficient diet (-Ile). See Chaveroux et al 2016

Key facts

Team

• Researchers : 21
• Technicians : 8
• Postdoc fellows : 1
• PhD Students : 9

Translational approaches

• Patents : 8
• Clinical research grants : 4
• Industry partnerships : 5

International research links

• Pr H Schiöth (Uppsala University)
• Pr T Hökfelt (Karolinska Institutet)
• Pr A Inui (Kagoshima University)

Keywords

• intestinal metabolism
• intestinal inflammation
• eating disorders
• Nutrients
• autoantibodies
• biomarkers
• innovative nutrition formulas
• immunonutrition
• neurostimulation

Biological Resources

• Cohorts of patients (IBS, IBD, eating disorders)
• Intestinal models: cell lines (HCT-8, Caco-2), human intestinal explants, experimental colitis

Pierre Déchelotte

Nutrition, inflammation and dysfunction of the brain-gut axis

University of Rouen Normand
Inserm U1073
Pierre Déchelotte
Rouen

Our research focuses on inflammatory bowel diseases and eating disorders performing translational research in close relationship between academic units, clinical departments and industrials to develop rapidely new therapeutics.

Research Brief :

The research of our group, integrated in the IRIB Institute, are mainly dedicated to the study of eating disorders, irritable bowel syndrome (IBS) and inflammatory bowel diseases (IBD). These pathologies share common features of intestinal inflammation and dysregulation of the gut-brain axis and offer great opportunities for innovative therapeutic strategies (immunonutrition, neurostimulation). Our projects explore the underlying mechanisms of these diseases from the molecular level to clinical trials. This broad range of research from the bench to the bedside is the result of our research strategy that brings together basic and clinical sciences, in a tight collaboration between laboratory scientists and health professionals. Our dynamic research team has an active research strategy which also drives the translation of research from the laboratory to patenting and creation of biotech company entrepreneurship (TargEdys).

• **Methodologies Used :**

Intestinal models: cell lines, human intestinal explants, experimental colitis
Proteomics: mass spectrometric analysis and in vivo isotopic studies
Body Composition in rodents and humans (DEXA)
Digestive function investigation platform (motility, sensitivity, endoscopy)
Neurostimulation and neuronavigation systems

Publications

Takagi K, Legrand R, Asakawa A, Amitani H, François M, Tennoune N, Coëffier M, Claeyssens S, do Rego JC, Déchelotte P, Inui A, Fetissov SO. (2013). Anti-ghrelin immunoglobulins modulate ghrelin stability and its orexigenic effect in obese mice and humans., Nat Commun. 4(), 2685

Gourcerol G, Tissier F, Melchior C, Touchais JY, Huet E, Prevost G, Leroi AM, Ducrotte P. (2015). . Impaired fasting pyloric compliance in gastroparesis and the therapeutic response to pyloric dilatation., Aliment Pharmacol Ther. 41(4), 360-7

Goichon A, Bertrand J, Chan P, Lecleire S, Coquard A, Cailleux AF, Vaudry D, Déchelotte P, Coëffier M. (2015). Enteral delivery of proteins enhances the expression of proteins involved in the cytoskeleton and protein biosynthesis in human duodenal mucosa., Am J Clin Nutr. 102(2), 359-67

Breton J, Tennoune N, Lucas N, Francois M, Legrand R, Jacquemot J, Goichon A, Guérin C, Peltier J, Pestel-Caron M, Chan P, Vaudry D, do Rego JC, Liénard F, Pénicaud L, Fioramonti X, Ebenezer IS, Hökfelt T, Déchelotte P, Fetissov SO., (2016). Gut Commensal E. coli Proteins Activate Host Satiety Pathways following Nutrient-Induced Bacterial Growth., Cell Metab. 23(2), 324-34

Belmonte L, Achamrah N, Nobis S, Guérin C, Riou G, Bôle-Feysot C, Boyer O, Richard V, Rego JC, Déchelotte P, Goichon A, Coëffier M. (2016). A role for intestinal TLR4-driven inflammatory response during activity-based anorexia., Sci Rep. 6(), 35813

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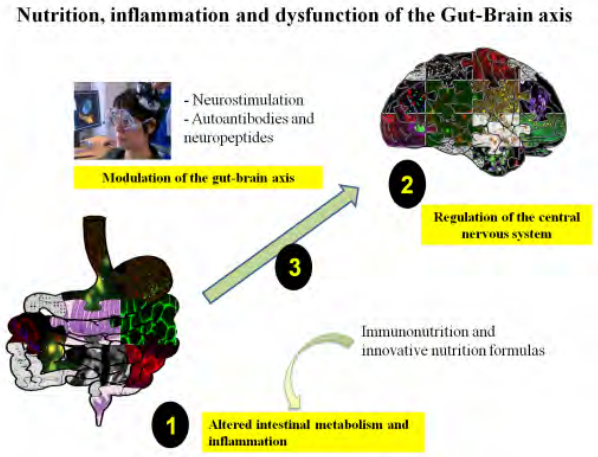
Nutrition, inflammation and dysfunction of the Gut-Brain axis



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C2VN Marseille Center for CardioVascular and Nutrition research

Patrick Borel

Human Micronutrition

Aix-Marseille Université
INRA U1260 INSERM U1063
Marie-Christine Alessi
Marseille

Our main objective is to study the impact of lipid micronutrients (mainly vitamins and carotenoids) on etiology of vascular and cardiometabolic diseases. We are the only team able to study both the fate of these compounds from the meal to their site of action as well as their health effects.

Key facts

Team

- Researchers : 15
- Technicians : 16
- Postdoc fellows : 0
- PhD Students : 7

Translational approaches

- Patents : 0
- Clinical research grants : 10
- Industry partnerships : 14

International research links

- Spain
- Hungary
- Luxembourg

Keywords

- Obesity
- Nutrigenetic
- Fat-soluble vitamins
- Adipose tissue
- Nutrigenomic
- Health effects
- Carotenoids
- Bioavailability
- Metabolomics
- Clinical studies
- Molecular biology
- Cell culture
- Preclinical studies

Biological Resources

- Intestinal and adipose tissue cell lines
- Clinical studies in nutrition
- Animal experiments in rodents (including transgenic mice)
- in vitro digestion model

Research Brief :

Numerous lines of evidence suggest that lipid micronutrients (LM: mainly fat soluble vitamins, carotenoids and phytosterols) have beneficial effects on several degenerative diseases including cardiovascular diseases. This can be explained by the fact that vitamin E and carotenoids exhibit antioxidant properties, phytosterols diminish cholesterol absorption, and vitamins D, E and carotenoids inhibit inflammation. However the bioavailability of these compounds is very low, it is affected by numerous factors (from the effect of the food matrix to the effect of genetic variations in genes involved in their absorption) and it is very variable among individuals. The objective of the team will be to assess the effects of LM and lipids on metabolic deteriorations that participate in the etiology of vascular and cardiovascular diseases, e.g. obesity, inflammation and insulin sensitivity, taking into account the factors that govern and affect their bioavailability and their metabolism. This will be done thanks to an integrative biology approach that uses complementary models, from in vitro digestion models to clinical studies through cell cultures, wild-type or transgenic animals and metabolomic. These objectives not only meet the INRA strategic research policies, stating that in-depth knowledge is required on the relationships between food, nutrition, prevention and health, but also those of the Food and Nutrition thematic area of the ALLEnvi Alliance and those of the PMN ITMO.

- **Methodologies Used :**

Animal experiments
Cell culture
GC-MS
HPLC
Intervention studies on healthy subjects and on insulin resistant subjects (obese, type 2 diabetic and subjects with metabolic syndrome)
Molecular biology
Multivariate analysis
Stable isotope kinetic studies

Publications

Reboul E, Borel P (2011). Proteins involved in uptake, intracellular transport and basolateral secretion of fat-soluble vitamins and carotenoids by mammalian enterocytes., Progress in lipid research. 50(4), 388-402

Goncalves A, Margier M, Roi S, Collet X, Niot I, Goupy P, Caris-Veyrat C, Reboul E. (2014). Intestinal scavenger receptors are involved in vitamin K1 absorption., J Biol Chem. 289(44), 30743-52

Borel P, Desmarchelier C, Nowicki M, Bott R, Morange S, Lesavre N (2014). Interindividual variability of lutein bioavailability in healthy men: characterization, genetic variants involved, and relation with fasting plasma lutein concentration., Am J Clin Nutr. 100(1), 168-75

Padilla N, Maraninchi M, Béliard S, Berthet B, Nogueira JP, Wolff E, Nicolay A, Bégu A, Dubois N, Grangeot R, Mattei C, Vialettes B, Xiao C, Lewis GF, Valéro R. (2014). Effects of bariatric surgery on hepatic and intestinal lipoprotein particle metabolism in obese, nondiabetic humans, Arterioscler Thromb Vasc Biol. 34(10), 2330-7

Borel P, Desmarchelier C, Nowicki M, Bott R, Tourniaire F. (2015). Can genetic variability in alpha-tocopherol bioavailability explain the heterogeneous response to alpha-tocopherol supplements?, Antioxid Redox Signal. 22(8), 669-78

Landrier JF, Kasiri E, Karkeni E, Mihály J, Béke G, Weiss K, Lucas R, Aydemir G, Salles J, Walrand S, de Lera AR, Rühl R (2017). Reduced adiponectin expression after high-fat diet is associated with selective up-regulation of ALDH1A1 and further retinoic acid receptor signaling in adipose tissue., Faseb J. 31(1), 203-211

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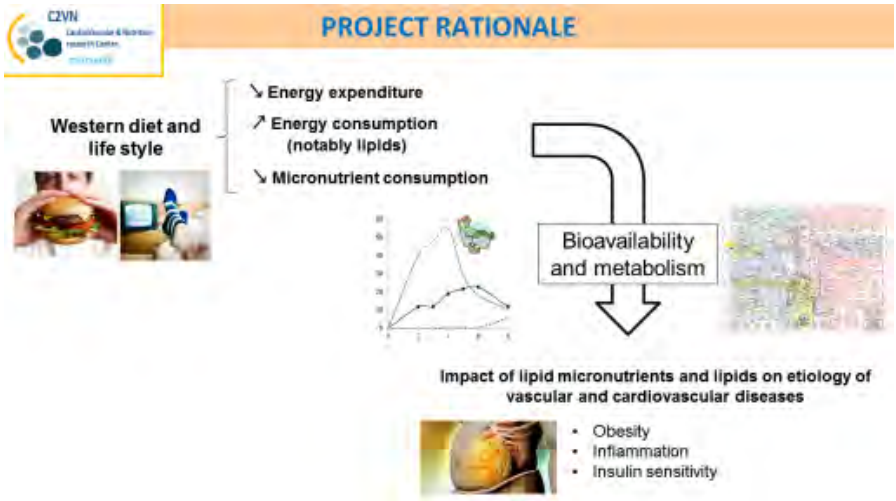
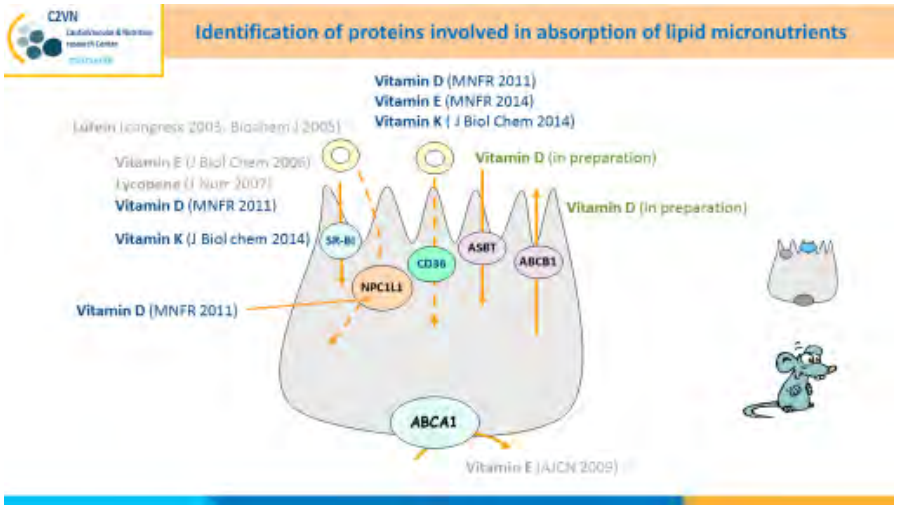
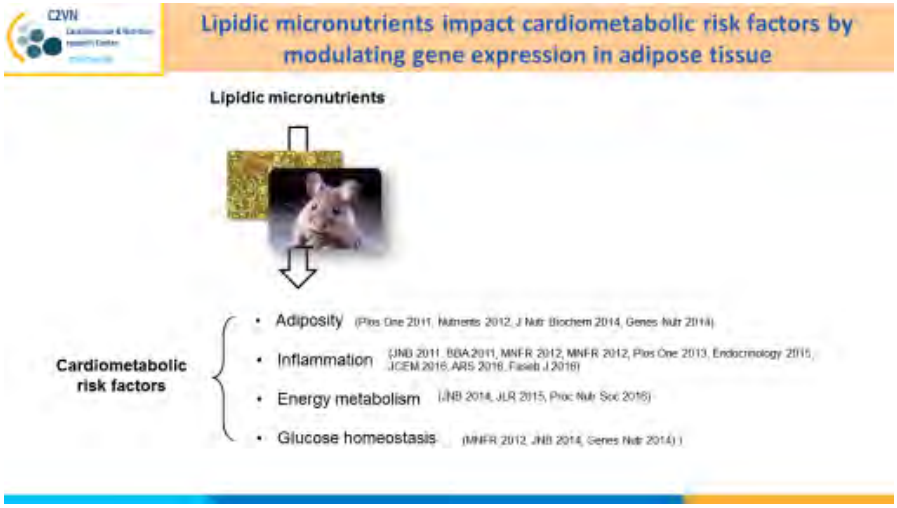


Western diet is associated to a decrease of energy expenditure, an increase of energy consumption, and a decrease of micronutrient consumption. The aim of the team is to study the impact of lipid micronutrients and lipids on etiology of vascular and cardiovascular diseases. Because these micronutrients are poorly absorbed we will take into account both their bioavailability and their metabolism. We are able to study the fate of vitamins and micronutrients from the meal to the cell nucleus.



We were the first to show that SR-B1 is involved in apical uptake of a carotenoid and extended this result to other carotenoids and vitamins D, E and K. We also showed that NPC1L1 is involved in vitamin D uptake and that ABCA1 is involved in vitamin E basolateral efflux. Recently we have shown that CD36 can impact the absorption of vitamin E, D and K, and are currently investigating the role of ASBT and other ABC transporters. Besides, we investigate transporter molecular functioning.



We are one of the leading team in the world, working on the impact of lipidic micronutrients on adipose tissue biology and systemic consequences. We demonstrated that active derivates of vitamin D, carotenoids or vitamin A modulate gene expression in adipose tissue, leading to improvement of several risk factors such as adiposity, inflammation, energy metabolism or glucose homeostasis. These data pave the way for nutritional preventive approaches in the context of cardiometabolic diseases.

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Institut Valrose Biologie

Ez-Zoubir Amri

Cellular and molecular regulation of fat mass

Université Côte d'Azur
CNRS UMR 7277 Inserm U1091
Stéphane Noselli
Nice

Use of unique cellular model, human multipotent adipose-derived stem (hMADS) cells, which differentiate into white adipocytes and convert into functional brown adipocytes

Key facts

Team

- Researchers : 4
- Technicians : 0
- Postdoc fellows : 0
- PhD Students : 1

Translational approaches

- Patents : 2
- Clinical research grants : 1
- Industry partnerships : 0

Keywords

- human adipose derived stem cells
- Obesity
- differentiation
- brown/brite adipocytes
- oxytocin
- lipid metabolism
- microRNA
- gene expression
- Cell culture
- oxygen consumption

Biological Resources

- Human multipotent adipose tissue derived stem cells

Research Brief :

Obesity reached epidemic proportions with no satisfactory treatment so far. Furthermore weight gain and fat mass redistribution represent a worldwide problem with aging as a larger proportion of the adult population is at risk of developing obesity, osteoporosis and associated diseases. Development of new therapies to control fat mass and its associated diseases, will be of great interest in terms of public health.
The objectives of our research program deal with the regulation of fat mass by two complementary approaches that are i) to favor the recruitment of functional brown adipocytes to enhance energy expenditure and ii) to lower the recruitment of white adipocytes by studying the role of oxytocin.
In contrast to early contention, healthy adult humans possess active brown adipose tissue with a potential for metabolic significance. Identification of factors leading to increased mass/activity of human brown adipose tissue are of great interest for the treatment of overweight/obesity. For this purpose, we set up a unique cellular model, human multipotent adipose-derived stem (hMADS) cells, which differentiate into white adipocytes and are able to convert into functional brown adipocytes. Our first aim deals with the analysis of mechanisms of conversion of human white to brown adipocytes and to identify potential therapeutic targets. Our second aim focus on the oxytocin involvement in the control of fat mass and in its distribution between adipose depots in animal models.

- **Methodologies Used :**

-Molecular and cellular biology
- Cell signalling
- Primary cell culture
- Animal models

Publications

Beranger GE, Pisani DF, Castel J, Djedaini M, Battaglia S, Amiaud J, Boukhechba F, Ailhaud G, Michiels JF, Heymann D, Luquet S, Amri EZ (2014). Oxytocin reverses ovariectomy-induced osteopenia and body fat gain., Endocrinology. 155(4), 1340-52

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Pisani DF, Beranger GE, Corinus A, Giroud M, Ghandour RA, Altirriba J, Chambard JC, Mazure NM, Bendahhou S, Duranton C, Michiels JF, Frontini A, Rohner-Jeanrenaud F, Cinti S, Christian M, Barhanin J and Amri EZ (2016). The K+ channel TASK1 modulates beta-adrenergic response in brown adipose tissue through the mineralocorticoid receptor pathway, FASEB J. 30(2), 909

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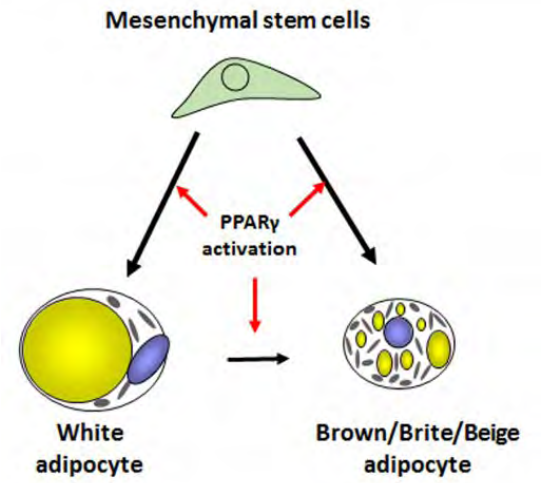
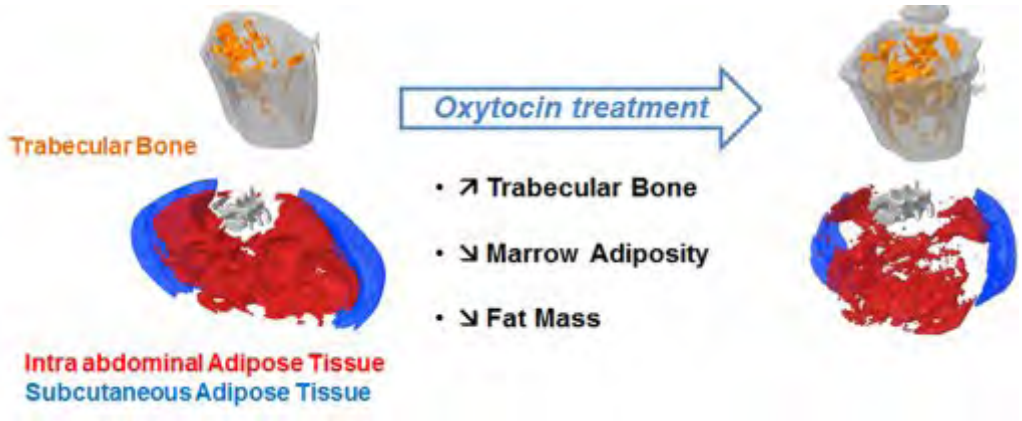
Converion of white to brite adipocyte



Oxytocin controls fat and bone mass



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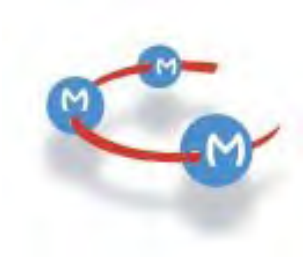

Jaap Neels

Adaptive responses to immuno-metabolic dysregulations

Université de Nice
Sophia-Antipolis
Inserm U1065
Patrick Auberger
NICE

Key facts

Team

- Researchers : 4
- Technicians : 1
- Postdoc fellows : 0
- PhD Students : 1

Translational approaches

- Patents : 1
- Clinical research grants : 0
- Industry partnerships : 0

Keywords

- obesity
- inflammation
- fatty acid metabolism
- immune T cells
- metabolic syndrome
- genomics
- cell biology
- transgenic
- biochemistry

Biological Resources

- Transgenic mice for tissue-specific expression of PPARb
- Genetically modified Jurkart T cells

Our goals are to understand the molecular mechanisms implicated in the adaptive responses to metabolic challenges of various tissues and cell types, to identify defects of these responses leading to metabolic disorders, and to explore new pharmacological approaches for metabolic diseases.

Research Brief :

In most industrialized countries, obesity has become epidemic, resulting in a dramatic rise of associated pathologies (e.g. diabetes, cardiovascular disease, asthma, Alzheimer's disease, and several forms of cancer). Growing evidence supports that the common denominator of these pathologic conditions is obesity induced low-grade inflammation. Our team's research efforts concentrate on the interplay between immunological and metabolic processes which has recently been defined as immunome¬tabolism; an emerging field of investigation at the interface between the historically distinct disciplines of immunology and metabolism. More specifically, our research focuses on the recently described role of adipose tissue T cells in the development of obesity-associated insulin resistance and type-2 diabetes. In particular, we are investigating the role of the ligand-activated nuclear receptor transcription factor Peroxisome Proliferator-Activated Receptor Beta (PPARbeta) in T cell biology in this context. We use both in vitro and in vivo models to study the role of PPARbeta in T cell proliferation / polarization, metabolism, mitochondria biogenesis/function, and oxidative stress. From these studies, we anticipate to obtain a better knowledge of the cellular and molecular mechanisms implicated in metabolic dysfunctions in obese/insulin resistant patients and to identify new targets for novel therapeutic approaches.

- **Methodologies Used :**

Mouse transgenics
Molecular and cellular biology
Biochemical and metabolic analyses
Nutritional and environmental interventions in animal models

Publications

Mothe-Satney I, Filloux C, Amghar H, Pons C, Bourlier V, Galitzky J, Grimaldi PA, Féral CC, Bouloumié A, Van Obberghen E, Neels JG (2012). Adipocytes secrete leukotrienes: contribution to obesity-associated inflammation and insulin resistance in mice., Diabetes. 61(9), 2311-9

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Rousseau AS, Sibille B, Murdaca J, Mothe-Satney I, Grimaldi PA, Neels JG (2016). ?-Lipoic acid up-regulates expression of peroxisome proliferator-activated receptor ? in skeletal muscle: involvement of the JNK signaling pathway, FASEB Journal. 30(3), 1287-99

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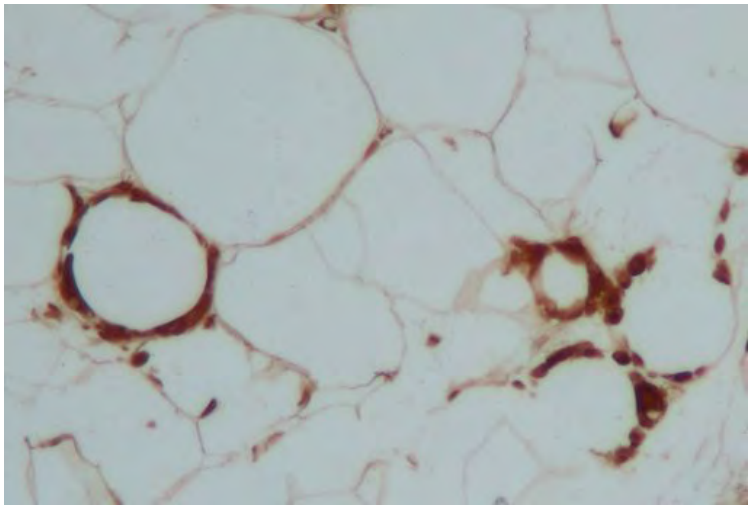
http://www.unice.fr/c3m/index.php/research-teams/team-9-adaptive-responses-to-immuno-metabolic-dysregulations/

T cells in adipose tissue



T cell staining (CD3) showing adipose tissue from an obese mouse with several adipocytes surrounded by T cells.

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http://www.unice.fr/c3m/index.php/research-teams/team-9-adaptive-responses-to-immuno-metabolic-dysregulations/

Mario Pende

Cell growth control by nutrients

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Xavier Nassif
Paris

Key facts

Team

- Researchers : 3
- Technicians : 2
- Postdoc fellows : 5
- PhD Students : 5

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 0

Keywords

- Growth
- Signal transduction
- mTOR
- Biochemistry
- Cell biology
- Mouse models

Biological Resources

- Mouse models

Functional studies to dissect the growth and metabolic control by signal transduction pathways

Research Brief :

In metazoans, nutrient and growth factor availability control cell number, size and metabolic homeostasis. We investigate the specific programs underlying these responses, and their coordination by signal transduction mechanisms.

- **Methodologies Used :**

Mouse models of cancer and metabolic diseases
Metabolomics
Genome editing
Viral vectors
Signal transduction
Autophagy flux
Translation

Publications

Espeillac C., Mitchell C., Celton-Morizur S., Chauvin C., Koka V., Gillet C., Albrecht J.H., Desdouets C., Pende M. (2011). S6 kinase 1 activity is required for rapamycin-sensitive liver proliferation after mouse hepatectomy, Journal of Clinical Investigation. (),

Panasyuk G., Espeillac C., Chauvin C., Pradelli L.A., Horie Y., Suzuki A., Annicotte J.S., Fajas L., Foretz M., Verdeguer F., Pontoglio M., Ferré P., Scoazec J.Y., Birnbaum M.J., Ricci J.E., Pende M. (2012). PPAR? contributes to PKM2 and HK2 expression in fatty liver., Nature Communications. (),

Liang N., Zhang C., Dill P., Panasyuk G., Pion D., Koka V., Gallazzini M., Olson E.N., Lam H., Henske E.P., Dong Z., Apte U., Pallet N., Johnson R.L., Terzi F., Kwiatkowski D.J., Scoazec J-Y., Martignoni G., Pende M. (2014). Regulation of YAP by mTOR and autophagy reveals a therapeutic target of tuberous sclerosis complex., Journal of Experimental Medicine. (),

*Class III PI3K regulates organismal glucose homeostasis by providing negative feedback on Nemazanyy I., Montagnac G., Russell R.C., Morzyglod L., Burnol A.F., Guan K.L., Pende M. *, Panasyuk G. hepatic insulin signalling. (2015). Class III PI3K regulates organismal glucose homeostasis by providing negative feedback on hepatic insulin signalling., Nature Communications. (),*

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BFA BIOLOGIE FONCTIONNELLE & ADAPTATIVE

Serge Luquet

Central Control of Feeding Behaviour and Energy Expenditure C2OFFEE

Université de Paris 07
(Université Denis Diderot)
CNRS UMR 8251
Jean-Marie Dupret
Paris

Fully integrated approaches are combined with genetic tools to study the mechanism that link the central nervous system with the regulation of energy balance and peripheral glucose metabolism.

Key facts

Team

• Researchers : 4
• Technicians : 4
• Postdoc fellows : 3
• PhD Students : 1

Translational approaches

• Patents : 0
• Clinical research grants : 0
• Industry partnerships : 7

International research links

• Germany
• USA
• Netherland

Keywords

• energy balance regulation
• central nervous system
• Mice model for neuron-specific cell knock out
• euglycemic hyperisulinemic clamp study

Biological Resources

• -Mice model for conditional inactivation of the N-acylphosphatidylethanolamine phospholipase-D (NAPE-PLD), a key enzyme in the processing of endocannabinoid and N-acyl ethanolamide such as oleoylethanolamide (OEA).
• -Mice model for conditional expression of Peroxisome Proliferator-Activated Receptors delta (PPARd) or a dominant negative form of this receptor

Research Brief :

The core approach of my research group C2OFFEE (http://www.bfa.univ-paris-diderot.fr/spip.php?rubrique81&lang=en) is to leverage the power of modern molecular genetic tools and mouse models in integrated approaches in order to dissect out the role of discrete neural circuit elements in the control of different aspect of energy balance including feeding behavior notably in its rewarding & motivational component together with energy expenditure and nutrient partitioning. A recent achievement was to identify a novel role for a hypothalamic circuitry in AgRP-neurons in the coordination of efferent organ activity and nutrient partitioning, providing a mechanistic link between obesity and obesity-related disorders. In addition we recently demonstrated that when AgRP-neurons ?activity is compromised through genetic, pharmacologic or dietary intervention (such as diet-induced obesity)-feeding behaviour is no longer dependent on metabolic demands but prominently rely on dopamine-encoded reward and leads to compulsive/comfort feeding. Finally we also highlighted a unique mechanism by which nutritional lipids can directly act on the brain to modulate food reward as a possible mechanism for addictive-like behaviour associated with high fat diet.

• **Methodologies Used :**

- Viral-mediated genetic modification of brain nuclei through stereotactic approaches, optogenetic and pharmacogenetic approaches
- Neurons-specific depletion (genetic engineering of Diphtheria receptor specific expression)
- In vivo indwelled chronic perfusion (carotid & jugular vein, intracerebroventricular)
- In vivo analysis of insulin sensitivity (euglycemic hyperinsulinemic clamp, insulin tolerance test)
- Microsurgery (catheter, cannula implant, vagal deafferentation, bariatric surgery in mice)
- In vivo assessment of motivated behaviour and positive reinforcement (conditioned place preference and operant behaviour)
- In vivo assessment of metabolic efficiency and energy balance using integrated indirect calorimetry

Publications

Joly-Amado A, Denis RG, Castel J, Lacombe A, Cansell C, Rouch C, Kassis N, Dairou J, Cani PD, Ventura-Clapier R, Prola A, Flamment M, Foufelle F, Magnan C, Luquet S (2012). Hypothalamic AgRP-neurons control peripheral substrate utilization and nutrient partitioning., The EMBO journal. 31(22),

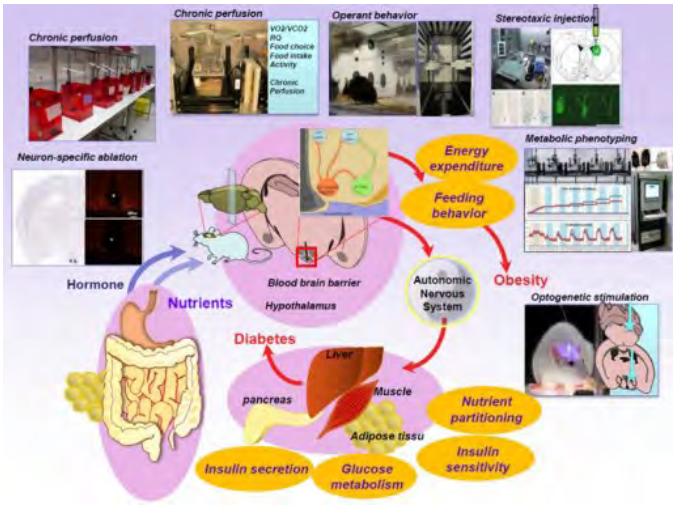
*(*2nd co Authorship). Langlet, F., Levin, B.E*., Luquet, S*., Mazzone, M*., Messina, A*., Dunn-Meynell, A.A., Balland, E., Lacombe, A., Mazur, D., Carmeliet, P., Bouret, S.G., Prevot, V., and Dehouck, B. (2013). Tanycytic VEGF-A Boosts Blood-Hypothalamus Barrier Plasticity and Access of Metabolic Signals to the Arcuate Nucleus in Response to Fasting, Cell Metabolism. 17(607),*

Geurts, L., Everard, A., Van Hul, M., Essaghir, A., Duparc, T., Matamoros, S., Plovier, H., Castel, J., Denis, R.G., Bergiers, M., Druart, C., Alhouayek, M., Delzenne, N.M., Muccioli, G.G., Demoulin, J.B., Luquet, S., and Cani, P.D. (2014). Intestinal epithelial MyD88 is a sensor switching host metabolism during diet induced obesity, Nature communications. 5(5648),

Cansell, C., Castel, J., Denis, R., Rouch, C., Delbes, AS., Martinez, S., Mestivier, D., Finan, B., Maldonado-Aviles, J.G, Rijnsburger, M., Tschöp, M.H., DiLeone, R.J., Eckel, R.H., La Fleur, S., Magnan, C., Hnasko, T., Luquet., S (2014). GRP78 expression inhibits insulin and ER stress-induced SREBP-1c activation and reduces hepatic steatosis in mice., Mol Psychiatry. 19(1095),

Denis, RG., Joly, A., Webber, E., Langlet, F., Schaeffer, M., Padilla, S., Cansell, C., Dehouck, B., Castel, J., Delbes, AS., Martinez, S.,Lacombe, A., Rouch, C., Kassis, N., Fehrentz,J-A., Martinez, J, Verdié, P., Hnasko, T, Palmiter, RD., Krashes, MJ., Güler, A., Magnan, C., Luquet, S (2015). Palatability can drive feeding independent of AgRP neurons, Cell Metabolism. 22(646),

C2OFFE team main Technic & goals



The core approach of my research group C2OFFEE (http://www.bfa.univ-paris-diderot.fr/spip.php?rubrique81&lang=en) is to leverage the power of modern molecular genetic tools and mouse models in integrated approaches in order to dissect out the role of discrete neural circuit elements in the control of different aspect of energy balance including feeding behavior notably in its rewarding & motivational component together with energy expenditure and nutrient partitioning.

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Key facts

Team

- Researchers : 8
- Technicians : 3
- Postdoc fellows : 5
- PhD Students : 1

Translational approaches

- Patents : 2
- Clinical research grants : 2
- Industry partnerships : 3

Keywords

- Atherosclerosis
- Vascular cells
- Immune cells
- Lipoproteins
- Lipids
- Lipid sensors/receptors
- Inflammation
- Immunity
- Macrophages
- Dendritic cells
- Apoptosis
- Postprandial
- Development of mouse models for cardiometabolic diseases
- Axenic mice, faecal transfert.
- Lipidomic, Metabolomic
- Metabolic phenotyping of mouse models
- Reverse cholesterol transport in vivo and in vitro.

Biological Resources

- Cohorts of dyslipidemic patients,
- Bank of mRNA from human Monocytes,
- Experimental models of atherosclerosis,
- Genetically-modified mice (tg CD68-hBcl2, tg CD11c-hBcl2, SR-BI flox/flox, ABCG1 flox/flox)

Philippe Lesnik

Integrative biology of cardiovascular and metabolic diseases

Université de Paris 06
(Université Pierre et Marie Curie)
Inserm
Stéphane Hatem
Paris

Expertise in lipoprotein metabolism, atherosclerosis, vascular diseases and mononuclear phagocytes.

Research Brief :

Our research goals are based on the premise that lipid-related inflammation and the associated immune responses are dominant components in atherogenesis. The underlying pathogenesis involves an imbalance of lipid and lipoprotein metabolism and a maladaptive immune response entailing a chronic inflammation of the arterial wall. The validity of this premise is becoming increasingly stronger as basic and clinical data demonstrate disturbed equilibrium of lipid metabolism and immune responses and resolution, shaped by lipoprotein retention, leukocyte trafficking and homeostasis. Our research focus on the clarification of cellular and molecular mechanisms of such lipido-inflammatory and immune responses, with a goal that new diagnostic and therapeutic approaches will emerge from this work. Indeed new reliable biomarkers allowing monitoring of the critical stages of vascular remodeling and thereof of potential complications are urgently required.

Novel molecular mechanisms, translational development and clinical strategies for studying lipid-related inflammation in atherosclerosis and vascular disease represent three major axes of our research program

Axe 1: To determine how lipids lipoproteins and immune cells crosstalk to influence atherogenesis
Axe 2: To assess the clinical relevance of novel mechanisms, genes, and biomarkers by studies of human diseases
Axe 3: To develop novel therapeutic strategies for inflammatory and metabolic disorders and atherosclerosis.

- **Methodologies Used :**

Development of mouse models for cardiometabolic diseases.
Metabolic phenotyping of mouse models.
Transcriptomic, Lipidomic, Metabolomic, Metagenomic, Epigenomic, Multivariate analysis.
Phenotyping and quantification of circulating and tissue leucocytes: flow cytometry/cell sorting.
Reverse cholesterol transport in vivo and in vitro.
Axenic mice, Faecal transfert.

Publications

Gilibert S, Galle-Treger L, Moreau M, Saint-Charles F, Costa S, Ballaire R, Couvert P, Carrie A, Lesnik P and Huby T. (2014). Adrenocortical scavenger receptor class B type I deficiency exacerbates endotoxic shock and precipitates sepsis-induced mortality in mice, Journal of Immunology. 193(817), 826

Gautier EL, Ivanov S, Williams JW, Huang SC, Marcelin G, Fairfax K, Wang PL, Francis JS, Leone P, Wilson DB, Artyomov MN, Pearce EJ and Randolph GJ. (2014). Gata6 regulates aspartoacylase expression in resident peritoneal macrophages and controls their survival., J Exp Med. 211(1525), 1531

Frisdal E, Le Lay S, Hooton H, Poupel L, Olivier M, Alili R, Plengpanich W, Villard EF, Gilibert S, Lhomme M, Superville A, Miftah-Alkhair L, Chapman MJ, Dallinga-Thie GM, Venteclef N, Poitou C, Tordjman J, Lesnik P, Kontush A, Huby T, Dugail I, Clement K, Guerin M and Le Goff W (2015). Adipocyte ATP-binding cassette G1 promotes triglyceride storage, fat mass growth, and human obesity., Diabetes. 64(840), 855

Bouchareychas L, Pirault J, Saint-Charles F, Deswaerte V, Le Roy T, Jessup W, Giral P, Le Goff W, Huby T, Gautier EL and Lesnik P (2015). Promoting macrophage survival delays progression of pre-existing atherosclerotic lesions through macrophage-derived apoE., Cardiovasc Res.. 108(111), 123

Du XM, Kim MJ, Hou L, Le Goff W, Chapman MJ, Van Eck M, Curtiss LK, Burnett JR, Cartland SP, Quinn CM, Kockx M, Rye KA, Kritharides L, Jessup and W. Kontush A, (2015). HDL particle size is a critical determinant of ABCA1-mediated macrophage cellular cholesterol export., Circ Res. 116(1133), 1142

Gall J, Frisdal E, Bittar R, Le Goff W, Bruckert E, Lesnik P, Giral P and Guerin M (2016). Association of Cholesterol Efflux Capacity With Clinical Features of Metabolic Syndrome: Relevance to Atherosclerosis, J Am Heart Assoc. 1161(1), 13

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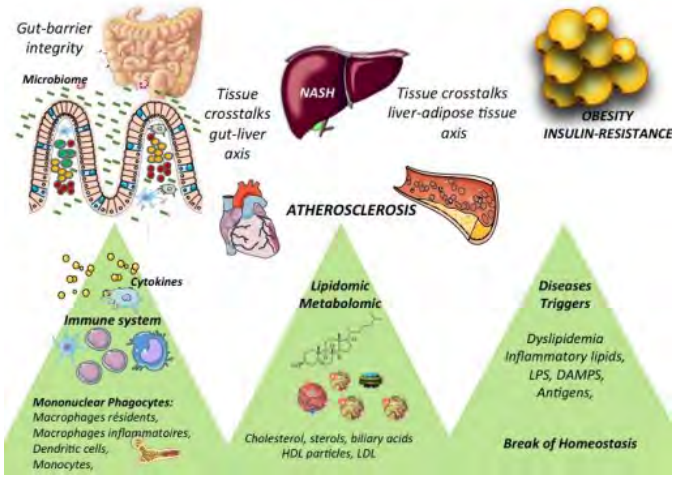
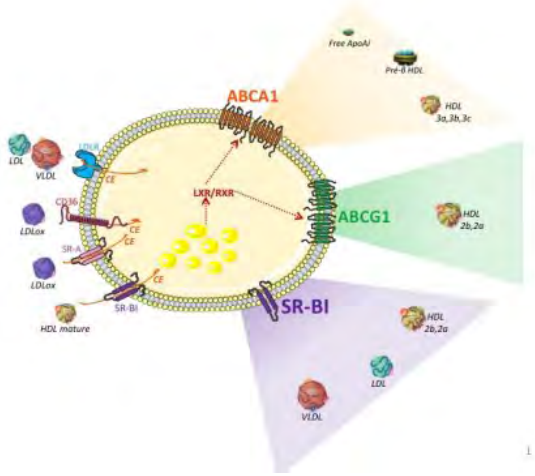
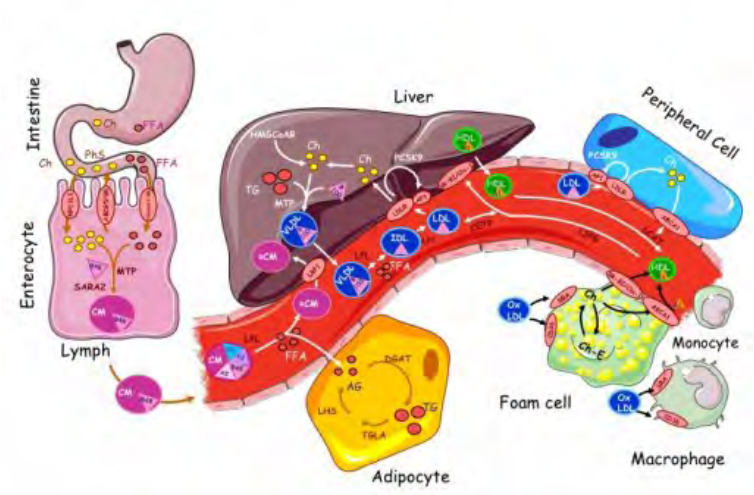
BENEFICIAL OR DETRIMENTAL IMPACT OF LIPID & MONONUCLEAR PHAGOCYTES ON METABOLIC DISORDERS



CHOLESTEROL HOMEOSTASIS IN MONONUCLEAR MACROPHAGES



OVERVIEW OF THE LIPOPROTEIN METABOLISM



Lesnik Philippe - philippe.lesnik@upmc.fr - www.insermu1166.fr

Key facts

Team

• Researchers : 14
• Technicians : 8
• Postdoc fellows : 4
• PhD Students : 4

Translational approaches

• Patents : 3
• Clinical research grants : 5
• Industry partnerships : 5

International research links

• METACARDIS
• Epos
• CMDO (Canada)

Keywords

• Nutrition
• Inflammation
• Microbiota
• Obesity
• Fibrosis
• IHC
• Cell culture
• Data mining and integration
• Trancriptomics, (meta)genomics
• animal models

Biological Resources

• Peripheral and portal blood
• urine and feces
• DNA, RNA banks (human and bacteria)
• Tissues (adipose tissue depots, liver, intestine)
• PBMC, adipose cells, Immune cells

Karine Clement

Nutriomique Team

Université de Paris 06
(Université Pierre et Marie Curie)
Inserm U1166
Stéphane Hatem
Paris

> ***Targeting obesity: From bench to bedside.***

Research Brief :

Nutriomics team is focused on the understanding of the patho-physiological mechanisms associated with obesity at its different stages of its natural progression. Since obesity is now recognized as a systemic disorder, the Nutriomics team develops and combines large-scale approaches with innovative bioinformatics and complex systems modeling tools in samples collected from well-phenotyped obese subjects with various metabolic disorders and disease stages. This strategy generates hypotheses on putative new cellular and molecular actors, further investigated by in vitro and ex vivo models and generated knockout mice models. By using these approaches, we identified and proved unexpected capacities of adipose tissue i) to accumulate immune cells, ii) to drive low-grade inflammation and iii) to promote extracellular matrix remodeling and fibrosis, which directly contribute to obesity and its complications. More recently NutriOmic team investigated the importance of environmental changes including nutritional switches on human metabolism and inflammation via modification of the gut microbiota. This last transversal theme uses bioinformatics approaches with multilevel data integration to ensure exploitation of research results towards the identification of signatures associated with obesity and comorbidity stages. Nutriomics is composed of an interactive group of multi-disciplinary PhD, MD-PhD scientists who work in the state-of-the-art facilities.

• **Methodologies Used :**

2D and 3D Cell cultures, migration, proliferation, differentiation
Cell biology (western blots, RT-PCR, immunofluorescence, confocal microscopy)
Immunochemistry, cell sorting FACS
siRNAs transfection, ChIPs, microarray
Bioinformatics : predictive analysis, network analysis, data integration, data mining
Physiology in animal models, genetically modified animals
Metagenomics, genomics, Genotyping, metabolomics, lipidomics
clinical investigation

Publications

Furet JP, Kong LC, Tap J, Poitou C, Basdevant A, Bouillot JL, Mariat D, Corthier G, Doré J, Henegar C, Rizkalla S, Clément K (2010). Differential adaptation of human gut microbiota to bariatric surgery-induced weight loss: links with metabolic and low-grade inflammation markers., Diabetes. 59(12), 3049-57

Bedossa P, Poitou C, Veyrie N, Bouillot JL, Basdevant A, Paradis V, Tordjman J, Clement K (2012). Histopathological algorithm and scoring system for evaluation of liver lesions in morbidly obese patients., Hepatology (Baltimore, Md.). 56(5), 1751-9

Toubal A, Clément K, Fan R, Ancel P, Pelloux V, Rouault C, Veyrie N, Hartemann A, Treuter E, Venteclef N (2013). SMRT-GPS2 corepressor pathway dysregulation coincides with obesity-linked adipocyte inflammation., The Journal of clinical investigation. 123(1),

Cotillard A, Kennedy SP, Kong LC, Prifti E, Pons N, Le Chatelier E, Almeida M, Quinquis B, Levenez F, Galleron N, Gougis S, Rizkalla S, Batto JM, Renault P, ANR MicroObes consortium , Doré J, Zucker JD, Clément K, Ehrlich SD (2013). Dietary intervention impact on gut microbial gene richness., Nature. 500(7464), 585-8

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Marcelin G, Ferreira A, Liu Y, Atlan M, Aron-Wisnewsky J, Pelloux V, Botbol Y, Ambrosini M, Fradet M, Rouault C, Hénégar C, Hulot JS, Poitou C, Torcivia A, Nail-Barthelemy R, Bichet JC, Gautier EL, Clément K (2017). A PDGFR-Mediated Switch toward CD9(high) Adipocyte Progenitors Controls Obesity-Induced Adipose Tissue Fibrosis., Cell Metab. 15(8), 940U144

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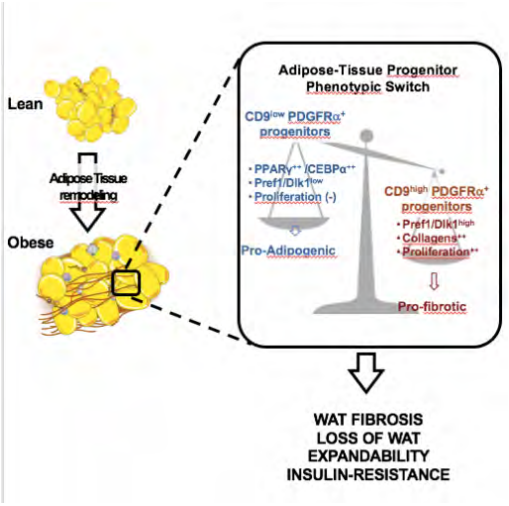
PDGFRa+ progenitors and fibrosis in adipose tissue



In obese subjects, white adipose tissue (WAT) fibrosis represents a maladaptive mechanism contributing to the loss of metabolic fitness and obesity-associated comorbidities. Marcelin et al. demonstrate that elevated PDGFRa+ progenitor subsets with high expression of CD9 promote WAT fibrosis and associate with metabolic deteriorations.
Marcelin et al, Cell Metal 2017

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http://www.ican-institute.org/team/umr_s872team-7-nutriomics-nutrition-obesity-systemic-approaches/

Key facts

Team

- Researchers : 2
- Technicians : 0
- Postdoc fellows : 0
- PhD Students : 1

Translational approaches

- Patents : 1
- Clinical research grants : 0
- Industry partnerships : 1

International research links

- USA, The Netherlands

Keywords

- pharmacological therapy
- respiratory chain
- fatty acid beta-oxydation
- mitochondria
- hereditary deficiency
- measurements of metabolic fluxes
- human muscle cells
- isolated mitochondria
- measurements of oxygen consumption
- measurements of enzyme activities

Fatima Djouadi Jean Bastin

Inborn mitochondrial disorders: pharmacological therapy and metabolic signaling

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Robert Barouki
Paris

Expertise in testing natural compounds, synthetic molecules, and already existing drugs for pharmacological therapy of inborn mitochondrial disorders in patient cells, using a personalized, genotype-based approach

Research Brief :

Our objective is to identify drugs or natural compounds which could be beneficial for correction of inborn fatty acid ß-oxidation (FAO) or respiratory chain (RC) defects, a large group of genetic disorders associated to life-threatening presentations, or to milder late-onset phenotypes, without treatment in most cases. We favor a pre-clinical approach performed in patients' cells (fibroblasts, myoblasts, myotubes) representing different enzymes defects associated to various mutations/genotypes. Our rationale is to test candidate molecules selected for their potential to stimulate or mitochondrial functions, in order to see if exposure to these molecules can improve residual FAO or RC capacities in panels of patients cells. We already proved that bezafibrate, a widely prescribed hypolipidemic drug, can correct mild FAO or RC deficiencies by activation of PPAR nuclear receptors, both ex-vivo in fibroblasts, and through a pilot clinical trial in FAO-deficient patients. Later on, resveratrol, a natural plant polyphenol, was also found to potentially correct mild FAO or RC deficiencies through complex metabolic signaling pathways involving the ERR orphan receptor and the PGC1alpha transcription co-activator. Presently, we focus on screening in patient cells the effects of natural (berberine, quercetin) or synthetic (AICAR, metformin, thiazolidinediones) compounds that potentially target the AMP-activated protein kinase, a major sensor and regulator of energy metabolism.

• Methodologies Used :

Measurements of metabolic fluxes (tritiated palmitate oxidation and oxygen consumption rates) in cultured patients' fibroblasts and myoblasts/myotubes. Pharmacological screening of selected compounds by dose-response and kinetics studies in control and in patients'cells. Relation genotype/pharmacological responses, genotype-based pharmacological screening. Determination of substrates' concentrations (glucose, lactate, NAD/NADH, etc...) and enzyme assays (Krebs cycle, pentose-P pathway, respiratory chain complexes, antioxidant enzymes, etc...) by spectrophotometric and fluorimetric methods in 96-well plates. Quantitative PCR, Western-blot, immunoprecipitation,

Publications

Bonnefont JP, Bastin J, Behin A, Djouadi F. (2009). Bezafibrate for treatment of an inborn mitochondrial ß-oxidation defect, N. Engl. J. Med. 360(:), 838-840

S. Gobin-Limballe, R. McAndrew, F. Djouadi, J.J. Kim and J. Bastin (2010). Compared effects of missense mutations in Very Long Chain Acyl-CoA Dehydrogenase deficiency: combined analysis by structural, functional and pharmacological approaches, BBA-Molecular Basis of Disease. 1802(:), 478-484

JP Bonnefont, J Bastin* (*contribution égale), P Laforêt, F Aubey, A Mogenet, S Romano, D Ricquier, S Gobin-Limballe, A Vassault, A Behin, B Eymard, JL Bresson, F Djouadi (2010). Long-term follow-up of bezafibrate treatment in the myopathic form of Carnitine-PalmitoylTransferase 2 deficiency, Clin Pharmacol Ther. 88(:), 101-108*

Alexandra Lopes Costa, Carole Le Bachelier, Lise Mathieu, Agnès Rotig, Avihu Boneh, Pascale De Lonlay, Mark A Tarnopolsky, David R Thorburn, Jean Bastin and Fatima Djouadi (2014). Beneficial effects of Resveratrol on respiratory chain defects in patients? fibroblasts involve estrogen receptor and estrogen-related receptor ??signaling, Hum. Mol. Genet. 23(:), 2106-2119

Aires V, Delmas D, Le Bachelier C, Latruffe N, Schlemmer D, Benoist JF, Djouadi F, Bastin J. (2014). Stilbenes and resveratrol metabolites improve fatty acid oxidation defects in human fibroblasts., Orphanet J Rare Dis. 9(1), 79

Mathieu L, Costa AL, Le Bachelier C, Slama A, Lebre AS, Taylor RW, Bastin J, Djouadi F. (2016). Resveratrol attenuates oxidative stress in mitochondrial Complex I deficiency : involvement of SIRT3, Free Radic Biol Med. 96(X), 190-198

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Key facts

Team

- Researchers : 9
- Technicians : 3
- Postdoc fellows : 0
- PhD Students : 4

Translational approaches

- Patents : 0
- Clinical research grants : 2
- Industry partnerships : 5

International research links

- Wageningen University
- SCIC, Madrid
- Birmingham University

Keywords

- Food reward
- Satiety
- Glucose homeostasis
- Energy metabolism
- Protein digestion and metabolism
- Metabolic and ingestive behaviour phenotyping
- Molecular biology
- Indirect calorimetry
- Stable isotopes
- Imagery

Biological Resources

- Human volunteers
- Primary cell culture
- Rodent models

Claire Gaudichon

Protein metabolism, energy homeostasis and ingestive behavior

Paris-Saclay AgroParisTech
INRA UMR0914
Daniel Tomé
Paris

Our team addresses the influence of quality and quantity of protein intake on metabolic, physiological and behavioral responses, using a large panel of approaches (metabolic fluxes by the way of tracers and calorimetry, molecular biology, neurobiology) in rodents and humans.

Research Brief :

Protein intake plays an important role in protein and energy homeostasis. Quantity and quality of protein influence the regulation of protein pathways in different tissues (intestine, liver, muscle, kidney, brain, ..) and also interact with glucose and lipid homeostasis, subsequently affecting lean and adipose tissue distribution. Dietary proteins are also involved in different signals interfering with dietary intake, either directly through homeostatic centers or indirectly through food reward. Our team studies the different pathways by which protein intake interacts with caloric intake and with protein and energy metabolism to achieve homeostasis.
In the past years, we provided important integrative knowledge on the adaptive responses to high protein diets that had been proposed as strategies in weigh management. We currently address the consequences of low protein intake on energy homeostasis, given that protein resources are worldwide a main concern for food insecurity.
Moreover, our team is recognized for its strong expertise in the in vivo assessment of protein quality depending on the protein source as well as technological treatments.
Clinical studies are mostly realized in the Research Human Nutrition Center, in Bobigny. Rodent studies are realized in our own animal care facility.

- **Methodologies Used :**

*In vivo exploration of protein digestion and metabolism as well as energy metabolism, using isotopic tracers, gastrointestinal tubes and indirect calorimetry
* Exploration of signaling pathways, especially in intestine, liver and brain, using classical molecular approaches and genetic models
* Phenotyping of ingestive behavior and metabolism using multiscale criteria in rodents
* Development of obesity resistant and prone rodent models
* Exploration of satiety and food reward system using imagery and psychobiological approaches in humans

Publications

Fromentin C, Tomé D, Nau F, Flet L, Luengo C, Azzout-Marniche D, Sanders P, Fromentin G, Gaudichon C. (2013). Dietary proteins contribute little to glucose production, even under optimal gluconeogenic conditions in healthy humans., Diabetes. 62(5), 1435-42

Marsset-Baglieri A, Fromentin G, Airinei G, Pedersen C, Léonil J, Piedcoq J, Rémond D, Benamouzig R, Tomé D, Gaudichon C. (2014). Milk protein fractions moderately extend the duration of satiety compared with carbohydrates independently of their digestive kinetics in overweight subjects., Br J Nutr. 112(4), 557-64

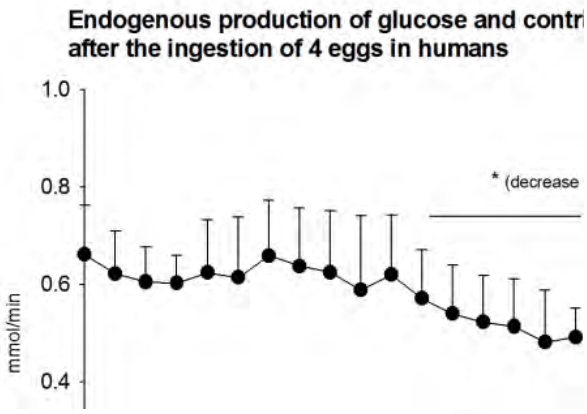
Davidenko O, Delarue J, Marsset-Baglieri A, Fromentin G, Tomé D, Nadkarni N, Darcel N. (2015). Assimilation and contrast are on the same scale of food anticipated-experienced pleasure divergence., Appetite. 90(), 160-7

Oberli M, Marsset-Baglieri A, Airinei G, Santé-Lhoutellier V, Khodorova N, Rémond D, Foucault-Simonin A, Piedcoq J, Tomé D, Fromentin G, Benamouzig R, Gaudichon C. (2015). High True Ileal Digestibility but Not Postprandial Utilization of Nitrogen from Bovine Meat Protein in Humans Is Moderately Decreased by High-Temperature, Long-Duration Cooking.., J Nutr. 145(10), 2221-8

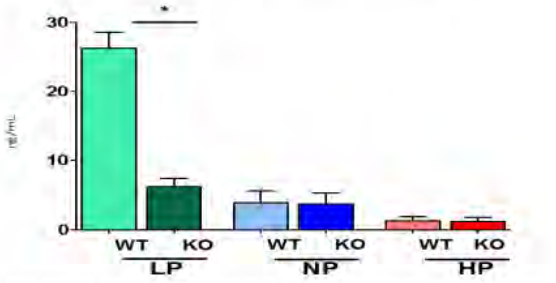
Azzout-Marniche D, Chalvon-Demersay T, Pimentel G, Chaumontet C, Nadkarni NA, Piedcoq J, Fromentin G, Tome D, Gaudichon C, and Even PC (2016). Obesity-prone high-fat fed rats reduce caloric intake and adiposity and gain more fat-free mass when allowed to self-select protein from carbohydrate:fat intake., Am J Physiol Regul Integr Comp Physiol. 310(11), R1169-76

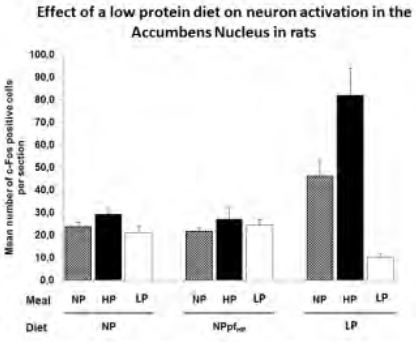
Chalvon-Demersay T, Even PC, Tomé D, Chaumontet C, Piedcoq J, Gaudichon C, Azzout-Marniche D. (2016). Low-protein diet induces, whereas high-protein diet reduces hepatic FGF21 production in mice, but glucose and not amino acids up-regulate FGF21 in cultured hepatocytes., J Nutr Biochem. 36(), 60-67

Gaudichon Claire - claire.gaudichon@agroparistech .fr - 33 1 44 08 18 29 - http://www6.jouy.inra.fr/pnca/Presentation-de-l-Unite



Effect of protein intake on FGF-21 secretion in wildtype or GCN2-KO mice





Rats were fed a normal (NP), or a low protein diet (LP). When they receive acutely a NP, high protein (HP) or LP meal, rats that were fed the LP diet had an increased number of c-Fos positive of neurons in the Accumbens Nucleus in response to NP or HP meal. We concluded that a low protein diet activates reward circuit in response to protein meal.

Chaumontet et al, in progress

Gaudichon Claire - claire.gaudichon@agroparistech .fr - 33 1 44 08 18 29 - http://www6.jouy.inra.fr/pnca/Presentation-de-l-Unite

Key facts

Team

• Researchers : 6
• Technicians : 1
• Postdoc fellows : 0
• PhD Students : 3

Translational approaches

• Patents : 0
• Clinical research grants : 0
• Industry partnerships : 1

Keywords

• Metabolic syndrome, Protein, Amino acids, Compartmental modelling, Isotopomic
• Metabolic and functional explorations in patients and rodents, Mass spectrometry and stable isotopes at natural abundance (isotopic signatures) or enriched levels (metabolic tracers), Compartmental modelling,

Biological Resources

• Human volonteers
• Rodent models
• Cohorts

Francois Mariotti

Protein intake, nutritional security, and cardiometabolic risk.

AgroParisTech Université Paris Saclay
INRA UMR0914
Claire Gaudichon
Paris

Using a translational approach from rodent models to clinical studies, our team aims to understand the links between protein and amino acid intake, amino acid metabolism and the early homeostatic dysregulations underlying the initiation of the metabolic syndrome.

• **Methodologies Used :**
- Metabolic and functional explorations in patients and rodents
- Mass spectrometry and stable isotopes at natural abundance (isotopic signatures) or enriched levels (metabolic tracers)
- Cell culture
- Compartmental modelling
- Biochemical and molecular studies (qPCR, western blotting, multiplex immunoassays, HPLC, reductive chemiluminescence).

Publications

De Gavelle, E; Huneau, J.-F.; Mariotti, F. (208). Patterns of Protein Food Intake Are Associated with Nutrient Adequacy in the General French Adult Population, Nutrients. 2(10),

Poupin, H., N.; Huneau, J.-F.; Mariotti, F.; Tomé, D.; Bos, C.; Fouillet (2013). Isotopic and modeling investigation of long-term protein turnover in rat tissues, American Journal of Physiology. Regulatory, Integrative and Comparative Physiology. 304(3), R218 ? R231

Galmiche, D., G.; Huneau, J.-F.; Mathe, V.; Mourot, J.; Simon, N.; Le Guillou, C.; Hermier (2016). n-3 Fatty acids preserve muscle mass and insulin sensitivity in a rat model of energy restriction, British Journal of Nutrition. 116(7), 1141-1152

Deveaux, F., A.; Pham, I.; West, S. G.; André, E.; Lantoine Adam, F.; Bunouf, P.; Sadi, S.; Hermier, D.; Mathe, V.; Fouillet, H.; Huneau, J.-F.; Benamouzig, R.; Mariotti (2016). L-Arginine supplementation alleviates postprandial endothelial dysfunction when baseline fasting plasma arginine concentration is low: a randomized controlled trial in healthy overweight adults with cardiometabolic risk factors, Journal of Nutrition. 146(7), 1330-130

Bianchi, C. M.; Huneau, J.-F.; Barbillon, P.; Lluch, A.; Egnell, M.; Fouillet, H.; Verger, E. O.; Mariotti, F. (2018). A clear trade-off exists between the theoretical efficiency and acceptability of dietary changes that improve nutrient adequacy during early pregnancy in French women: combined data from simulated changes modeling and online assessment survey, Plos One. 4(13),

Mariotti Francois - francois.mariotti@agroparistec h.fr

Key facts

Team

• Researchers : 3
• Technicians : 6
• Postdoc fellows : 4
• PhD Students : 1

Translational approaches

• Patents : 0
• Clinical research grants : 0
• Industry partnerships : 0

International research links

• Belgium - United Kingdom - Switzerland - The Netherlands

Keywords

• Adipose tissue
• Lymphocytes
• Psoriasis
• Fc receptors
• Type 2 diabetes
• Nuclear receptors
• Atherosclerosis
• Inflammation
• Obesity
• Immune cells
• NASH
• Eosinophils
• Histology and Immunohistochemistry
• Flow and mass cytometry
• Pharmacology
• Genetically-modified mice
• Invasive and non invasive plethysmography
• Real-time PCR

Biological Resources

• Genetically-modified mice (hFcepsilonRIalpha Tg, FcepsilonRIalpha-/-, FcRbeta-/-, PPARbeta/gamma-/-, FXR-/-, RORalpha-/-)

David Dombrowicz

Nuclear receptors, immuno-inflammation and cardiometabolic diseases

Université de Lille
Institut Pasteur de Lille Inserm UMR1011
Bart Staels
Lille

Research is centered on the regulation, by nuclear receptors, of immune cell contribution to cardiovascular diseases, atherosclerosis and type 2 diabetes.

Research Brief :

Building on our experience in allergic diseases and the immuno-regulatory role of nuclear receptors in asthma and atopic dermatitis, we develop a research on immuno-inflammation in cardio-metabolic diseases, atherosclerosis and type 2 diabetes.

1. We study the regulation by FXR and RORalpha of immune cell functions as well as of the development of atherosclerosis using whole body or cell-specific deletion of these genes in mice and feeding with high fat western diet. Expression of these genes in distinct lymphoid subsets downregulate metabolic inflammation.

2. Using both experimental models and a translational approach, we investigate the link between psoriasis, an inflammatory skin disease, and cardiovascular disease. We demonstrate that high fat diet increases psoriasis severity by altering innate and adaptive immune response through metabolic reprogramming.

3. We characterize the impact of type 2 diabetes on blood and adipose tissue immune cell subpopulations in obese patients with Non Alcoholic SteatoHepatitis and correlate blood phenotype with clinico-biological parameters as well as adipose tissue and liver transcriptome.

• **Methodologies Used :**

Genetically-modified mice
Pharmacology
Histology and Immunohistochemistry
Flow cytometry
Real-time PCR
Invasive and non invasive plethysmography
Laser capture microdissection

Publications

Kanda A, Driss V, Hornez N, Abdallah M, Roumier T, Abboud G, Legrand F, Staumont-Sallé D, Quéant S, Bertout J, Fleury S, Rémy P, Papin JP, Julia V, Capron M, Dombrowicz D (2009). Eosinophil-derived IFN-gamma induces airway hyperresponsiveness and lung inflammation in the absence of lymphocytes., The Journal of Allergy and Clinical Immunology. 124(3), 573-82, 582.e1-9

Mionnet C, Buatois V, Kanda A, Milcent V, Fleury S, Lair D, Langelot M, Lacoeuille Y, Hessel E, Coffman R, Magnan A, Dombrowicz D, Glaichenhaus N, Julia V (2010). CX3CR1 is required for airway inflammation by promoting T helper cell survival and maintenance in inflamed lung., Nature Medicine. 16(11), 1305-12

Staumont-Salle D, Fleury S, Lazzari A, Molendi-Coste O, Hornez N, Lavogiez C, Kanda A, Wartelle J, Fries A, Pennino D, Mionnet C, Prawitt J, Bouchaert E, Delaporte E, Glaichenhaus N, Staels B, Julia V, Dombrowicz D (2014). CX3CL1 (fractalkine) and its receptor CX3CR1 regulate atopic dermatitis by controlling effector T cell retention in inflamed skin., The Journal of Experimental Medicine. 211(6), 1185-96

Julia V, Macia L, Dombrowicz D (2015). The impact of diet on asthma and allergic diseases., Nature Reviews Immunology. 15(5), 308-22

Wawrzyniak M, Pich C, Gross B, Schutz F, Fleury S, Quemener S, Sgandurra M, Bouchaert E, Moret C, Mury L, Rommens C, Mottaz H, Dombrowicz D, Michalik L* (*senior communicating authors) (2015). Endothelial, but not smooth muscle, peroxisome proliferator-activated receptor ?/? regulates vascular permeability and anaphylaxis., The Journal of Allergy and Clinical Immunology. 135(6), 1625-35*

Everaere L, Ait-Yahia S, Molendi-Coste O, Vorng H, Quemener S, Le Vu P, Fleury S, Bouchaert E, Fan Y, Duez C, De Nadai P, Staels B, Dombrowicz D, Tsicopoulos A* with an Editors'Editorial p. 1299 (*senior communicating authors) (2016). Innate lymphoid cells contribute to allergic airway disease exacerbation by obesity., The Journal of Allergy and Clinical Immunology. 138(5), 1309-18*

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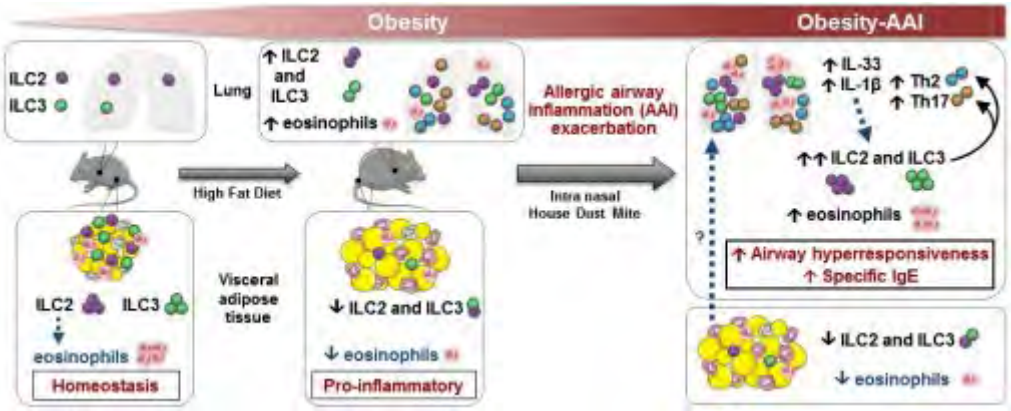
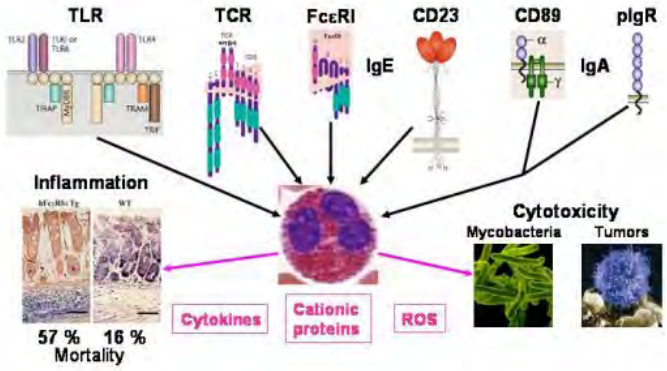
ILC in asthma exacerbation by obesity



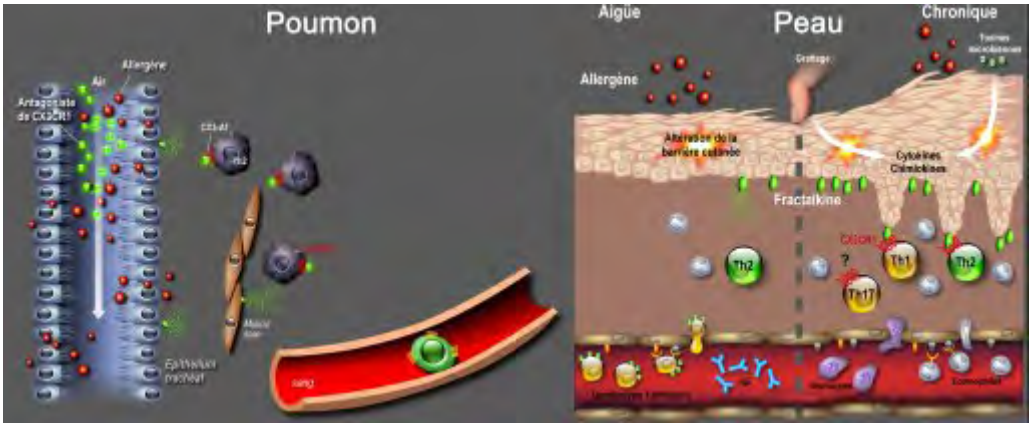
HFD feeding exacerbated allergic asthma. Obese mice show increased lung ILC and eosinophilia compared to lean mice. Lung ILC2 and ILC3 further increased in HDM-challenged obese mice compared to lean mice, with high IL-33 and IL-1? levels and decreased ILC markers in visceral adipose tissue. ILC depletions followed by T-cell reconstitution, led to a decrease in allergic asthma in obese mice, including TH2 and TH17 infiltration. (Julia et al. Nat. Rev. Immunol. 2015 & Everaere et al. JACI. 2016)

Receptor-induced eosinophil activation in inflammatory, infectious and oncologic diseases



Through release of cytotoxic mediators and cytokines, eosinophils exert a detrimental role in inflammatory diseases but are beneficial in immunity against helminths, mycobacteria and tumors. Cytotoxic and regulatory activities are triggered through the expression of several receptors associated to innate (TLR, TCRgammadelta) or acquired (FcR) immunity. (Decot et al. and Karagiannis et al. J. Immunol. 2005 and 2007; Legrand et al. PlosOne 2009; Driss et al. Blood 2009; Kanda et al. JACI. 2009)

Fractalkine and its receptor in allergic diseases



In lung and skin, antigen-specific Tcell migration is CX3CR1-independent.and CX3CR1 is only expressed once T cell reach the tissue. Interaction with CX3CL1, its unique ligand, expressed by epithelial or smooth muscle cells allows T cell survival within the inflamed lung while it regulates retention of Th1 and Th2 cells in skin. A CX3CR1 antagonist blocks survival signal and prevents airway hypereactivity and inflammation (Mionnet et al. Nat. Med. 2010 & Staumont-Salle et al. J. Exp. Med, 2014)

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Research teams with secondary association to PMN Institute

Key facts

Team

- Researchers : 3
- Technicians : 1
- Postdoc fellows : 1
- PhD Students : 4

Translational approaches

- Patents : 3
- Clinical research grants : 1
- Industry partnerships : 3

International research links

- italy
- Spain
- switzerland

Keywords

- Cytotoxic lymphocytes
- dichloroacetate
- immunotherapy
- ERK5
- Tolerance
- bone marrow transplantation
- in vivo models
- in vitro lymphocyte expansion

Biological Resources

- HEMODIAG: cohort from hematological neoplasias

Martin Villalba Gonzalez

Lymphocytes differentiation, tolerance and metabolism: basis for immunotherapy

University of Montpellier
INSERM 1183
Christian Jorgensen
montpellier

We have been the first to link tumor cell metabolism to tumor immune escape. We have developed an unique protocol to expand NK cells. We have identified antitumor cells in patients.

Research Brief :

We are interested on understanding how tumor cell metabolism affects tumor immune escape. The mostly glycolytic tumor metabolism generate the activation of intracellular signalling pathways that induces expression on the membrane of ligands for immune receptors. Therefore, it is possible to modulate tumor immune recognition by altering tumor metabolism. We also develop specific protocols to produce large numbers of cytotoxic lymphocytes, in particular natural killer (NK) cells. We use these cells to develop clinical trials.

- **Methodologies Used :**

Lymphocyte expansion
in vivomodels for lymphocyte infiltration
FACs 20 colors

Publications

Seyma Charni, Geoffroy de Bettignies, Moeez Ghani Rathore, Juan I. Aguiló, Peter J. van den Elsen, Delphine Haouzi, Robert A. Hipskind, José Antonio Enriquez, Margarita Sanchez-Beato, Julián Pardo, Alberto Anel and Martin Villalba (2010). Oxidative Phosphorylation induces de novo expression of the Major Histocompatibility Complex-I in tumor cells through de ERK5 pathway., J Immunol. S. 185(6), 3498

Martin Villalba, Moeez G. Rathore, Nuria Lopez-Royuela, Ewelina krzywinska, Johan Garaude and Nerea Allende-Vega. (2013). From tumor cell metabolism to tumor immune escape., The International Journal of Biochemistry and Cell Biology. 45(1), 106

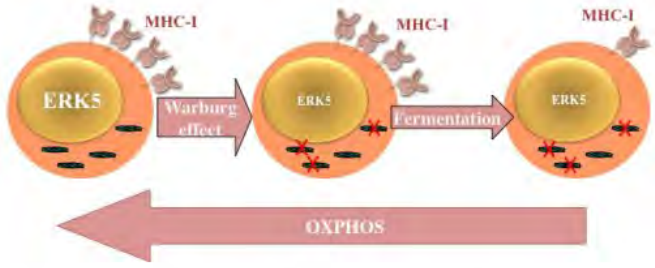
Ewelina Krzywinska, Nerea Allende-Vega, Amelie Cornillon, Dang-Nghiem Vo, Laure Cayrefourcq, Catherine Panabieres, Carlos Vilches, Julie Déchanet-Merville, Yosr Hicheri, Jean-François Rossi, Guillaume Cartron and Martin Villalba. (2015). Identification of anti tumor cells carrying natural killer (NK) cell antigens in patients with hematological cancers., EBioMedicine. 2(10), 1276

Nerea Allende-Vega, Ewelina Krzywinska, Stefania Orecchioni, Nuria Lopez-Royuela, Francesca Reggiani, Giovanna Talarico, Jean-François Rossi, Rodrigue Rossignol, Yosr Hicheri, Guillaume Cartron, Francesco Bertolini and Martin Villalba (2015). The presence of wild type p53 in hematological cancers improves the efficacy of combinational therapy targeting metabolism., Oncotarget. 6(22), 19228

Elena Catalán, Seyma Charni, Juan Ignacio Aguiló, José Antonio Enríquez, Javier Naval, Julián Pardo, Alberto Anel & Martín Villalba (2015). MHC-I modulation due to metabolic changes regulates tumor sensitivity to CTL and NK cells., Oncoimmunology. 4(1),*

Abrar Ul Haq Khan, Moeez G. Rathore, Nerea Allende-Vega, Dang-Nghiem Vo, Sana Belkhala, Stefania Orecchioni, Giovanna Talarico, Francesco Bertolini, Guillaume Cartron, Charles-Henri Lecellier and Martin Villalba. (2016). Human leukemic cells performing oxidative phosphorylation (OXPHOS) generate an antioxidant response independently of reactive oxygen species (ROS) generation., EBioMedicine. 3(1), 43

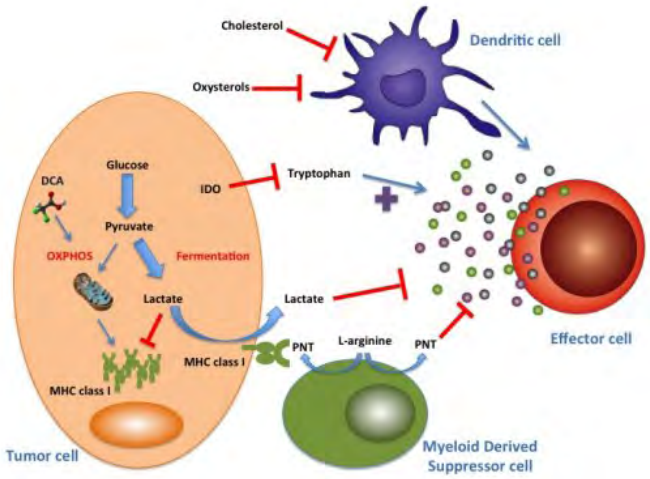
Tumor metabolism controls MHC-I expression.



Tumor metabolism controls MHC-I expression. Tumor cells choose glycolysis metabolism to generate ATP rather than mitochondrial metabolism even in the presence of oxygen (Warburg effect). The pyruvate generated in the glycolysis is reduced to lactate (fermentation). Surface expression of MHC-I is often reduced in tumor cells to avoid the immune attack. Oxidative phosphorylation (OXPHOS) induces expression of ERK5, which increases MHC-I expression at the transcription level.

Tumor cells choose glycolysis metabolism to generate ATP rather than mitochondrial metabolism even in the presence of oxygen (Warburg effect). The pyruvate generated in the glycolysis is reduced to lactate (fermentation). Surface expression of MHC-I is often reduced in tumor cells to avoid the immune attack. Oxidative phosphorylation (OXPHOS) induces expression of ERK5, which increases MHC-I expression at the transcription level.

Tumor cell metabolism protect them from immune cells



Co-regulation of metabolism and immune function to kill tumor cells.

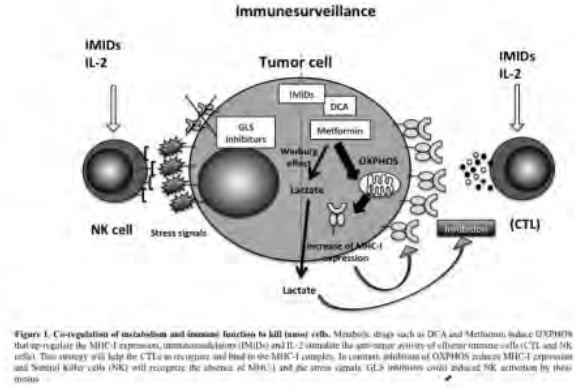


Figure 1. Co-regulation of metabolism and immune function to kill tumor cells. Metabolic drugs such as DCA and Metformin induce OXPHOS that up-regulate the MHC-I expression, immunomodulators (IMiDs) and IL-2 stimulate the anti-tumor activity of effector immune cells (CTL and NK cells). This strategy will help the CTLs to recognize and bind to the MHC-I complex. In contrast, inhibition of OXPHOS reduces MHC-I expression and Natural killer cells (NK) will recognize the absence of MHC-I and the stress signals. GLS inhibitors could induced NK activation by these means.

Metabolic drugs such as DCA and Metformin induce OXPHOS that up-regulate the MHC-I expression, immunomodulators (IMiDs) and IL-2 stimulate the anti-tumor activity of effector immune cells (CTL and NK cells).

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Gladys Mirey

Genotoxicity Signaling

Université Paul Sabatier -
Toulouse III
INRA UMR1331
Theodorou Vassilia
Toulouse

Association of DNA damage and DNA repair assays to study genotoxicity mechanisms, particularly after exposure to food contaminants.

Key facts

Team

- Researchers : 5
- Technicians : 1
- Postdoc fellows : 1
- PhD Students : 1

Translational approaches

- Patents : 1
- Clinical research grants : 0
- Industry partnerships : 1

International research links

- Europe (Sweden, Norway), United States (National Institute on Aging - NIH)

Keywords

- Genotoxicity/DNA damage
- Contaminants
- Signaling
- Metabolism
- DNA repair
- Genotoxicity assays
- Cell engineering
- Biotracers/Biosensors
- Repair systems/Biochemistry
- Biomonitoring

Biological Resources

- In vivo/in vitro genotoxic assays

Research Brief :

Our team studies the effects of various chemical (pesticides, nanoparticules) or biological (such as bacterial genotoxins) compounds present as contaminants in food, on the integrity of our DNA. We develop in particular cell assays and biotracers to characterize the genotoxicity mechanisms.

- **Methodologies Used :**

Molecular biology, Cell Biology, Biochemistry, Cell imaging & Cytometry (DNA damage, cell cycle, apoptosis), Genotoxicity assays (comet assay, micronucleus,...).

Publications

Fedor Y, Vignard J, Nicolau-Travers ML, Boutet-Robinet E, Watrin C, Salles B, Mirey G. (2013). From single-strand breaks to double-strand breaks during S-phase: a new mode of action of the Escherichia coli Cytolethal Distending Toxin., Cell Microbiol.. 15(1), 1-15

Lebailly P, Mirey G, Herin F, Lecluse Y, Salles B, Boutet-Robinet E. (2015). DNA damage in B and T lymphocytes of farmers during one pesticide spraying season., Int Arch Occup Environ Health.. 88(7), 963-72

Bezine E, Malaisé Y, Loeuillet A, Chevalier M, Boutet-Robinet E, Salles B, Mirey G, Vignard J. (2016). Cell resistance to the Cytolethal Distending Toxin involves an association of DNA repair mechanisms., Scientific Reports. (6), 36022

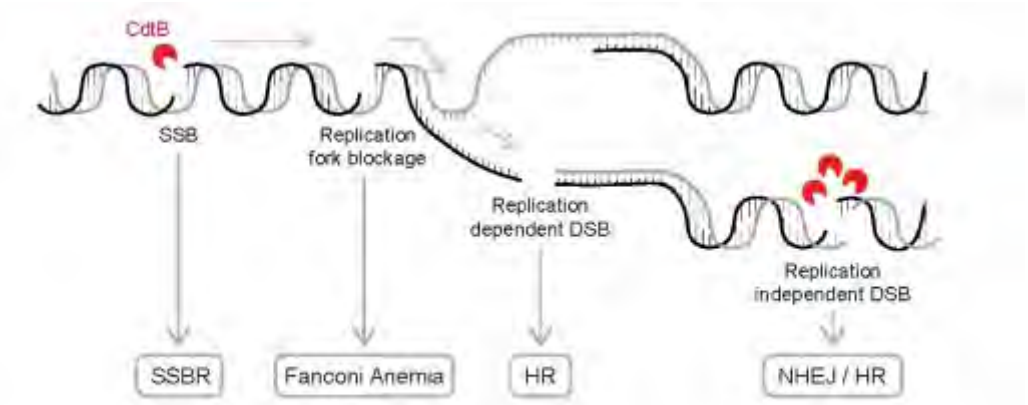
Graillot V, Dormoy I, Dupuy J, Shay JW, Huc L, Mirey G, Vignard J. (2016). Genotoxicity of Cytolethal Distending Toxin (CDT) on Isogenic Human Colorectal Cell Lines: Potential Promoting Effects for Colorectal Carcinogenesis., Front Cell Infect Microbiol.. (6), 34

Jullien D, Vignard J, Fedor Y, Béry N, Olichon A, Crozatier M, Erard M, Cassard H, Ducommun B, Salles B, Mirey G. (2016). Chromatibody, a novel non-invasive molecular tool to explore and manipulate chromatin in living cells., J Cell Science. 129(13), 2673-83

Bettini S, Boutet-Robinet E, Cartier C, Coméra C, Gaultier E, Dupuy J, Naud N, Taché S, Grysan P, Reguer S, Thieriet N, Réfrégiers M, Thiaudière D, Cravedi JP, Carrière M, Audinot JN, Pierre FH, Guzylack-Piriou L, Houdeau E. (2017). Food-grade TiO2 impairs intestinal and systemic immune homeostasis, initiates preneoplastic lesions and promotes aberrant crypt development in the rat colon., Scientific Reports. (7), 40373

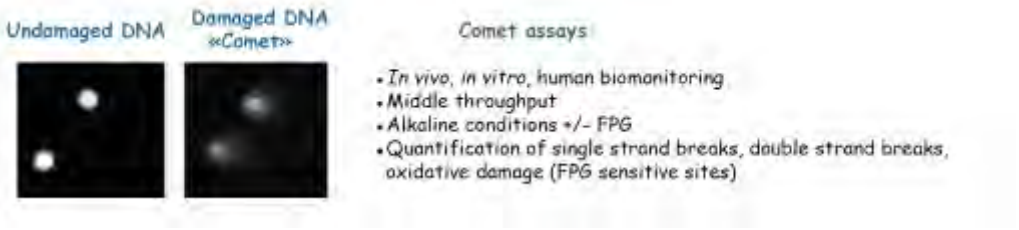
Mirey Gladys - gladys.mirey@inra.fr - +33 5 82 06 63 38 -
https://www6.toulouse.inra.fr/toxalim_eng/Research-Teams/E8-GS-Genotoxicity-Signaling/Research

A new mode of action for the Cytolethal Distending Toxin.



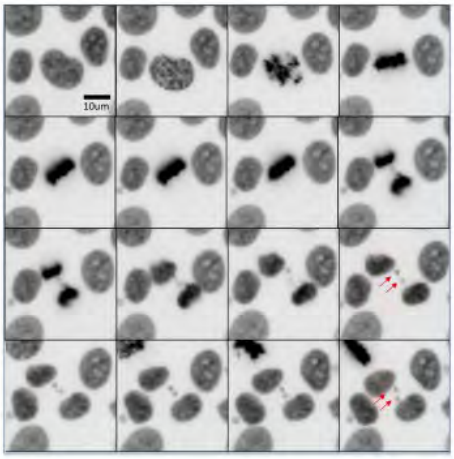
We used an association of DNA damage and DNA repair assays to revisit the Cytolethal Distending Toxin mode-of-action and showed the importance of replicative stress to generate DNA double-strand breaks (Fedor et al., Graillot et al., Bezine et al.).

Evaluation of DNA damage for biomonitoring and toxicological studies.



We develop different versions of comet assays in order to detect a large panel of DNA damage on various samples, for either biomonitoring or in vivo toxicological studies (Fedor et al., Lebailly et al., Bezine et al., Bettini et al.).

Real-time observation of micronuclei assay in metabolic-competent cells.



We are using metabolic-competent cells, expressing a chromatin biotracer (Jullien et al.), to study genotoxicity and micronucleus formation.

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https://www6.toulouse.inra.fr/toxalim_eng/Research-Teams/E8-GS-Genotoxicity-Signaling/Research

Key facts

Team

- Researchers : 7
- Technicians : 3
- Postdoc fellows : 1
- PhD Students : 3

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 0

Keywords

- membrane biology
- traffic
- lipid transfer
- membrane curvature
- polyunsaturated lipids
- biochemistry
- liposomes
- cell biology
- molecular dynamics

Bruno Antonny

Dynamics of lipid membranes and protein coats

Université de Nice - Sophia
Antipolis
CNRS UMR7275
Jean-Louis Nahon
Valbonne

Molecular approaches

Research Brief :

Various proteins remodel the membranes of organelles involved in intracellular transport. Protein coats deform membranes to promote the budding of vesicles. Golgins, sort of molecular strings, tether vesicles to restrict their diffusion. Lipid transporters adjust the membrane composition. Although very different, most of these mechanisms are controlled by small G proteins of the Arf family and by the physical chemistry of membranes.

We study these mechanisms through molecular, cellular and in silico approaches. With original assays based on fluorescence and light scattering, we follow elementary reactions such as the assembly cycle of protein coats, the tethering of liposomes by a golgin or the transfer of lipids. With fluorescence light microscopy and electron microscopy, we visualize these events in cells and in reconstituted systems. With molecular dynamics, we describe at the atomic level how specific protein motifs sense the chemistry and curvature of lipid membranes.

Recent findings
- Intracellular transport of cholesterol through the counter exchange of a phosphoinositide and its hydrolysis.
- Phospholipids with omega 3 acyl chains boost membrane deformation and fission
- Atomic description of the packing of lipids in membranes of various curvature and composition

• **Methodologies Used :**

Combination of molecular, cellular and in silico approaches.

Reconstitution experiments with liposomes to study and understand elementary reactions
Molecular dynamics simulations to understand the behavior of lipids in membranes

Publications

Mesmin B, Bigay J, Moser von Filseck J, Lacas-Gervais S, Drin G, Antonny B. (2013). A four-step cycle driven by PI(4)P hydrolysis directs sterol/PI(4)P exchange by the ER-Golgi tether OSBP, Cell. 155(), 830-43

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Pinot M, Vanni S, Pagnotta S, Lacas-Gervais S, Payet LA, Ferreira T, Gautier R, Goud B, Antonny B, Barelli H (2014). Polyunsaturated phospholipids facilitate membrane deformation and fission by endocytic proteins., Science. 345(), 693-7

Magdeleine M, Gautier R, Gounon P, Barelli H, Vanni S, Antonny B. (2016). A filter at the entrance of the Golgi that selects vesicles according to size and bulk lipid composition, eLife. 5(), e16988

Barelli H, Antonny B (2016). Lipid unsaturation and organelle dynamics, Curr Opin Cell Biol. 41(), 25-32

Antonny Bruno - antonny@ipmc.cnrs.fr - https://www.ipmc.cnrs.fr/cgi-bin/ipmcx.cgi

Key facts

Team

- Researchers : 2
- Technicians : 1
- Postdoc fellows : 1
- PhD Students : 3

Translational approaches

- Patents : 1
- Clinical research grants : 0
- Industry partnerships : 0

Keywords

- non-coding RNAs
- gene expression
- RNA metabolism
- inflammatory disorders
- epigenetics
- mass-spectrometry
- high throughput sequencing
- in vivo models
- bioinformatics
- epidemiology

Biological Resources

- mouse lines

Michele Trabucchi

CONTROL OF GENE EXPRESSION

Université de Nice
Sophia-Antipolis
Inserm 1065
Patrick Auberger
NICE

combination of biochemistry and bioinformatics approaches in the investogation of non-coding RNA in gene expression control

Research Brief :

we focused on discovering novel mechanisms of post-transcriptional events controlling gene expression. Particularly, since its creation the team has utilized several newly-emerging technologies to investigate the importance of the expression control and the mode of action of small RNAs in development and physiopathological events of metabolic disorders. We use different high-throughput experimental approaches, including mass-spectrometry and deep sequencing analysis coupled with bioinformatics, mouse models and epidemiological approaches. We have developed a series of important and complex stories to the point that they stand scrutiny at rigorous and prestigious journals, including Nature, Plos Genetics, BMC Medicine, Nucleic Acids Research, Cell Death & Disease, Nature Structural & Molecular Biology, and Nucleic Acids Research. In these papers, we described novel aspects of small RNA-dependent gene expression control, which shed a light of their central role in physiopathological events.

- **Methodologies Used :**

Mass-spectrometry; high-throughput sequencing; in vivo models; bioinformatics, epidemiology

Publications

Trabucchi M, Briata P, Garcia-Mayoral M, Haase AD, Filipowicz W, Ramos A, Gherzi R, Rosenfeld MG (2009). The RNA-binding protein KSRP promotes the biogenesis of a subset of microRNAs., Nature. 459(7249), 1010-4

Repetto E, Briata P, Kuziner N, Harfe BD, McManus MT, Gherzi R, Rosenfeld MG, Trabucchi M (2012). Let-7b/c enhance the stability of a tissue-specific mRNA during mammalian organogenesis as part of a feedback loop involving KSRP., PLoS genetics. 8(7), e1002823

Hu Q, Tanasa B, Trabucchi M, Li W, Zhang J, Ohgi KA, Rose DW, Glass CK, Rosenfeld MG (2012). DICER- and AGO3-dependent generation of retinoic acid-induced DR2 Alu RNAs regulates human stem cell proliferation, Nature structural & molecular biology. 19(11), 1168-75

E. Repetto, L. Lichtenstein, Z. Hizir, N. Tekaya, M. Benahmed, J.B. Ruidavets, L.E. Zaragosi, B. Perret, L. Bouchareychas, A. Genoux, R. Lotte, R. Ruimy, J. Ferrières, P. Barbry, L.O. Martinez, M. Trabucchi (2015). RNY-derived small RNAs as a signature of Coronary Artery Disease, BMC Medicine. 13(1), 259

S. Bottini, N. Hamouda-Tekaya, B. Tanasa, L.E. Zaragosi, V. Granjean, E. Repetto, M. Trabucchi (2017). From benchmarking HITS-CLIP peak detection programs to a new method for identification of miRNA-binding sites from Ago2-CLIP data, Nucleic Acids Research. (),

Z. Hizir, S. Bottini, V. Grandjean, M. Trabucchi#, E. Repetto# (2017). RNY-derived small RNAs promotes macrophage inflammation and cell death, Cell Death & Disease. 8(), e2530

Trabucchi Michele - mtrabucchi@unice.fr

Key facts

Team

• Researchers : 6
• Technicians : 4
• Postdoc fellows : 1
• PhD Students : 3

Translational approaches

• Patents : 0
• Clinical research grants : 0
• Industry partnerships : 3

International research links

• Chine
• Allemagne

Keywords

• gut microbiota, metabolic diseases, brain diseases, nutrition
• germ-free animal models, metagenomicsUMR

Biological Resources

• germ-free mice and rats

Philippe Gérard

Amipem

Université Paris Saclay
INRA UMR1319
Stéphane Aymerich
Jouy-en-Josas

Thanks to the unique tool constituted by the germfree facilities of the MICALIS institute, we developed strategies based on microbiota transfer (from animal models or human patients) to germfree rodents in order to prove the causal role played by the gut microbiota in metabolic and brain diseases.

Research Brief :

There is growing evidence that the gut microbiota and its bacterial genome (the microbiome), affect host? physiology. These findings raise the possibility that the gut microbiota plays a role in the susceptibility to develop pathologies.
In the AMIPEM team, our projects concern the study of the interaction between food and gut microbiota as a factor involved in the development of human pathologies. Thanks to the unique tool constituted by the germfree facilities of the MICALIS institute, we developed strategies based on microbiota transfer (from animal models or human patients) to germfree rodents in order to prove the causal role played by the gut microbiota in these pathologies. Using molecular analysis (including metagenomics) of the gut microbiota, analytical biochemistry and metabolomics, we also aim at identifying bacterial species, genes and metabolites associated with patho-physiological parameters. We also assess the effects of a microbiota modulation using pro or prebiotics on the considered pathologies. Our current projects more specifically target the role of the gut microbiota in the development of the metabolic diseases and in brain disorders.

• **Methodologies Used :**

. gnotobiology (germ-free animal models)
. metagenomics
. transcriptomics

Publications

Le Roy T, Llopis M, Lepage P, Bruneau A, Rabot S, Bevilacqua C, Martin P, Philippe C, Walker F, Bado A, Perlemuter G, Cassard-Doulcier AM, Gérard P. (2013). Intestinal microbiota determines development of non-alcoholic fatty liver disease in mice., Gut. (),

Crumeyrolle-Arias M, Jaglin M, Bruneau A, Vancassel S, Cardona A, Daugé V, Naudon L, Rabot S. (2014). Absence of the gut microbiota enhances anxiety-like behavior and neuroendocrine response to acute stress in rats., Psychoneuroendocrinology. (),

Llopis M, Cassard-Doulcier AM, Wrosek L, Boschat L, Ferrere G, Bruneau A, Puchois V, Martin JC, Lepage P, Le Roy T, Lefèvre L, Langelier B, Cailleux F, González-Castro AM, Rabot S, Gaudin F, Agostini H, Prévot S, Berrebi D, Ciocan D, Jousse C, Naveau S, Gérard P, Perlemuter G (2016). Intestinal microbiota contributes to individual susceptibility to alcoholic liver disease, Gut. (),

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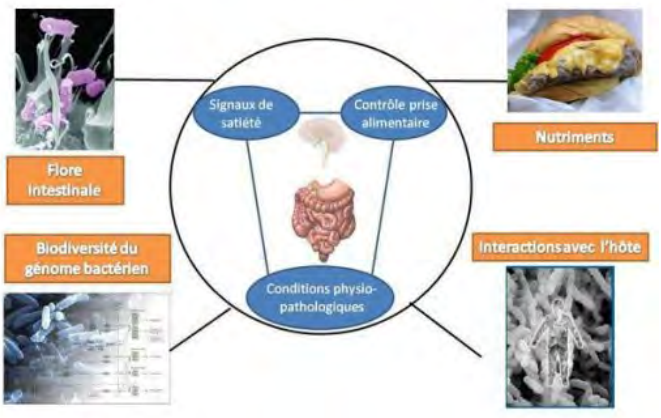


Key facts

Team

- Researchers : 1
- Technicians : 2
- Postdoc fellows : 4
- PhD Students : 1

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 0

Keywords

- antibiotics
- metallo-enzymes
- natural products
- Enzyme
- RiPP
- Crystallogenesis
- Mass spectrometry
- Biochemistry

Olivier Berteau

ChemSyBio

Université Paris Sud : Paris 11
INRA UMR1319
Stéphane Aymerich
Jouy en Josas

Our team uses biochemical and chemical approaches to solve the mechanism of novel enzymes.

Research Brief :

The ChemSyBio team is investigating novel enzymes catalysing unprecedented post-translational modifications. These enzymes use radical chemistry notably to produces various antibiotics, anti-cancer agents and toxins.

• Methodologies Used :

Mass spectrometry, structural biology.

Publications

Pierre, S., Guillot, A., Benjdia, A., Sandstrom, C., Langella, P., and Berteau, O. (2012). Thiostrepton tryptophan methyltransferase expands the chemistry of radical SAM enzymes, Nature Chemical Biology. 8(), 957

Benjdia, A., Pierre, S., Gherasim, C., Guillot, A., Carmona, M., Amara, P., Banerjee, R., and Berteau, O. (2015). The thiostrepton A tryptophan methyltransferase TsrM catalyses a cob(II)alamin-dependent methyl transfer reaction, Nature Communincations. 6(), 8377

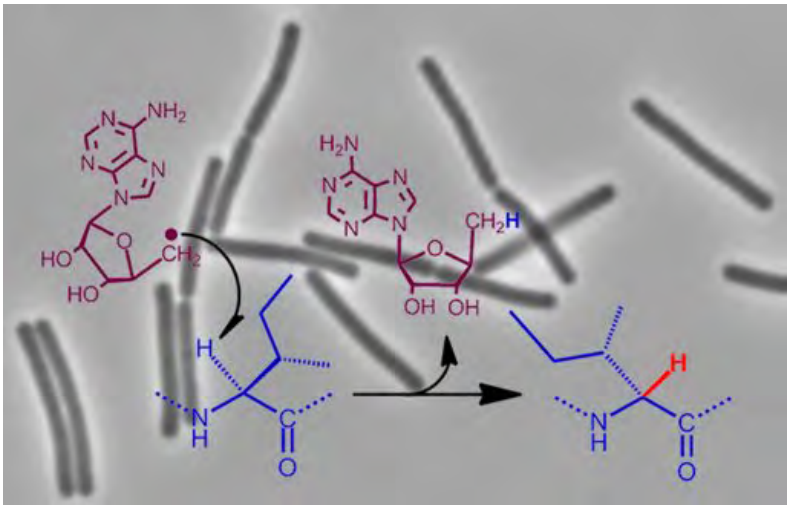
Philmus, B., Decamps, L., Berteau, O., and Begley, T. P. (2015). Biosynthetic versatility and coordinated action of 5'-deoxyadenosyl radicals in deazaflavin biosynthesis, J Am Chem Soc. 137(), 5406

Parent, A., Guillot, A., Benjdia, A., Chartier, G., Leprince, J., and Berteau, O (2016). The B12-Radical SAM Enzyme PoyC Catalyzes Valine Cbeta-Methylation during Polytheonamide Biosynthesis, J Am Chem Soc. 138(), 15515

Benjdia, A., Guillot, A., Lefranc, B., Vaudry, H., Leprince, J., and Berteau, O (2016). Thioether bond formation by SPASM domain radical SAM enzymes: Calpha H-atom abstraction in subtilosin A biosynthesis, Chem Commun. 52(), 6249

Benjdia, A., Guillot, A., Ruffié, P., Leprince, J., and Berteau, O (2017). Post-translational modification of ribosomally synthesized peptides by a radical SAM epimerase in Bacillus subtilis, Nature Chemistry. (),

Novel synthesis of post-translationally modified peptides



Stephen Manon

Mitochondria, Stress and Cell Death

Université de Bordeaux
CNRS UMR5095
Bertrand Daignan-Fornier
Bordeaux

Our team investigates the central role of mitochondria as both a mediator and a target of degradation processes involved in cellular quality control regulation.

- **Methodologies Used :**

- heterologous expression of human proteins of the Bcl-2 family in model systems
- study of post-translationnal process of Bcl-2 family members
- role of Bcl-2 family members in survival processes, both apoptosis and non-apoptosis related
- role of mitochondria metabolism, including lipid metabolism, in mitophagy
- molecular mechanisms underlying mitochondria permeabilization during apoptosis

Key facts

Team

• Researchers : 4
• Technicians : 1
• Postdoc fellows : 0
• PhD Students : 2

Translational approaches

• Patents : 0
• Clinical research grants : 0
• Industry partnerships : 0

International research links

• Slovakia
• Portugal
• USA

Keywords

• mitochondria
• apoptosis
• bcl-2 family
• mitophagy
• protein biochemistry
• heterologous expression
• cell biology
• mitochondria energetics
• reconstituted models

Biological Resources

• plasmid constructs for in vitro production of Bcl-2 family members
• human cancer cell lines, including KO-lines (HCT-116, HeLa, etc...)
• yeast mutants in mitochondria-related functions, expressing human proteins
• yeast mutants in autophagy-related processes

Publications

Deffieu M, Bhatia-Kissova I, Salin B, Klionsky DJ, Pinson B, Manon S, Camougrand N (2013). Increased cytochrome b reduction and mitophagy components are required to trigger nonspecific autophagy following induced mitochondrial dysfunction., J Cell Science. 126(), 415-426

Athané A, Buisson A, Challier M, Beaumatin F, Manon S, Bhatia-Kissova I, Camougrand N (2015). Insights into the relationship between the proteasome and autophagy in human and yeast cells., Int J Biochem Cell Biol. 64(), 167-173

Renault TT, Teijido O, Missire F, Ganesan YT, Velours G, Arokium H, Beaumatin F, Llanos R, Athané A, Camougrand N, Priault M, Antonsson B, Dejean LM, Manon S (2015). Bcl-xL stimulates Bax relocation to mitochondria and primes cells to ABT-737., Int J Biochem Cell Biol. 64(), 136-146

Beaumatin F, El Dhaybi M, Lasserre JP, Salin B, Moyer MP, Verdier M, Manon S, Priault M (2016). N52-monodeamidated Bcl-xL shows impaired oncogenic properties in vivo and in vitro., Oncotarget. 7(), 17129-17243

Simonyan L, Renault TT, da Costa Novais MJ, Sousa MJ, Côrte-Real M, Camougrand N, Gonzalez C, Manon S (2016). Regulation of Bax/mitochondria interaction by AKT., FEBS Lett. 590(), 13-21

Simonyan L, Légiot A, Lascu I, Durand G, Giraud MF, Gonzalez C, Manon S (2017). The substitution of Proline 168 favors Bax oligomerization and stimulates its interaction with LUVs and mitochondria., Biochim Biophys Acta. 1859(), 1144-1155

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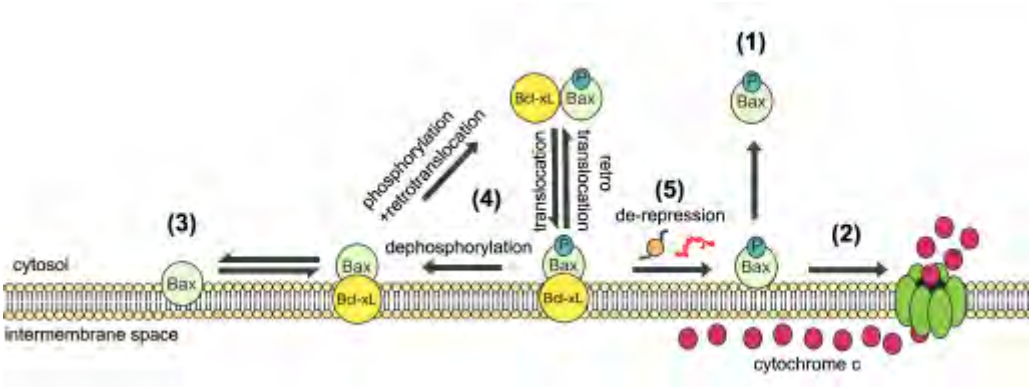
Schematic representation of the different steps of Bax activation



(1) Bax phosphorylation favors a cytosolic localization. (2)The small amount of Bax localized at the mitochondria may create MOMP. (3) When not phosphorylatable, Bax is MOM-localized but is poorly active. (4) In the presence of Bcl-xL, both Bax translocation and retrotranslocation occur, favoring a dynamic regulation of Bax activity. Phosphorylation and dephosphorylation contribute to this regulation. (5) The activity of MOM-localized Bax can be revealed with a BH3-mimetic drug.

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Yaël Grosjean

Sensory Perception, Interactions between Glia and Neurons

Université de Bourgogne Dijon AgroSup Dijon
CNRS UMR6265 INRA UMR1324
Lionel Brétillon
Dijon

We try to understand how chemicals (food odors and amino acids) are detected and processed into the brain to lead to a specific behavioral and/or physiological response, mainly focusing on glia/Neuron interaction through the study of a family of amino acid transporters.

Key facts

Team

• Researchers : 4
• Technicians : 3
• Postdoc fellows : 0
• PhD Students : 0

Translational approaches

• Patents : 0
• Clinical research grants : 0
• Industry partnerships : 0

Keywords

• drosophila
• glia/neuron interaction
• SLC7A amino acid transporters
• olfaction
• metabolism
• immunohistology
• molecular genetics
• calcium imaging
• biochemistry
• behavior

Biological Resources

• S2 cells
• Drosophila melanogaster

Research Brief :

Our surrounding environment is bathed in chemicals. They can be tasted, smelled and eaten. They represent vital information for the cells and the organism. Our team "Sensory Perception, Glia/Neuron Interactions" explores the molecular and cellular mechanisms allowing the perception of these chemical signals, and their effects on physiology and metabolism.

• **Methodologies Used :**

Basic research (molecular genetics, biochemistry, immunohistology, developmental assays, behavioral analyses) using Drosophila melanogaster as a biological model.

Publications

Grosjean Y., Rytz R, Farine J.P., Abuin L., Cortot J., Jefferis G.S.X.E. & Benton R. (2011). An olfactory receptor for food-derived odours promotes male courtship in Drosophila., Nature. 478(), 236-240

Silbering A.S., Rytz R.*, Grosjean Y.*, Abuin L., Ramdya P., Jefferis G.S.X.E. & Benton R. (2011). Functional neuroarchitecture and evolution of the Drosophila olfactory subsystems., Journal of Neuroscience. 31(), 13376-13385*

Ziegler A.B., Ménagé C., Grégoire S., Garcia T., Ferveur J.-F., Bretillon L. & Grosjean Y. (2015). Lack of Dietary Polyunsaturated Fatty Acids Causes Synapse Dysfunction in the Drosophila Visual System., PLoS One. 10(), e0135353

Manière G., Ziegler A.B., Geillon F., Featherstone D.E. & Grosjean Y. (2016). Direct Sensing of Nutrients via a LAT1-like Transporter in Drosophila Insulin-Producing Cells., Cell Reports. 17(), 137-148

Depetris-Chauvin A, Galagovsky D, Chevalier C, Maniere G & Grosjean Y. (2017). Olfactory detection of a bacterial short-chain fatty acid acts as an orexigenic signal in Drosophila melanogaster larvae., Scientific Reports. 7(), 14230

Ziegler A.B., Manière G.* & Grosjean Y. (2018). JhI-21 plays a role in Drosophila insulin-like peptide release from larval IPCs via leucine transport., Scientific Reports. 8(), 1908*

Key facts

Team

• Researchers : 5
• Technicians : 2
• Postdoc fellows : 0
• PhD Students : 1

Translational approaches

• Patents : 0
• Clinical research grants : 0
• Industry partnerships : 0

International research links

• Japan
• Germany

Keywords

• olfactory receptor and olfactory neurons
• central olfactory areas
• neuroplasticity
• rodents
• Transgenic mice
• Connectomics using PRV viruses
• Electrophysiology (patch-clamp, EOG)
• Olfactory receptor expression in heterologous systems and functional assays
• Pharmacogenetics

Xavier Grosmaitre

Olfactory neuroplasticity and feeding behaviors

Université de Dijon
(Université de Bourgogne)
CNRS UMR6265 INRA UMR1324
Lionel Bretillon
Dijon

We perform electrophysiological recordings of mammalian olfactory sensory neurons in transgenic mice; we analyze the plasticity of these neurons during development, under the influence of the environment and the nutritional status of the animal.

Research Brief :

Our goal is to investigate how the olfactory system evolves during development and neurogenesis as well as under the influence of the odorant environment and internal metabolic signals. We are using rodents as our main experimental model. We are investigating different levels of modulation, from olfactory receptors to central areas of the brain. We develop molecular, cellular, anatomical and physiological techniques as well as behavioral assays.
Main research topics:
1: Functional properties of olfactory receptors and olfactory sensory neurons;
2: Odorant induced plasticity in olfactory neurons: consequences of the odorant environment on the properties of olfactory neurons;
3: Plasticity of the olfactory system induced by homeostatic changes: effects of nutritional status and diet. We evaluate the effects of diet on the physiology of the olfactory system (peripheral and central levels) and olfactory behaviors. We use different types of diet inducing metabolic disorders.
4: Neural structures involved in olfactory, hedonic and feeding behaviors: connections, plasticity and behavioral impact.
We use stereotactic injections of retrograde tracers such as polysynaptic virus (PRV) and monosynaptic cholera toxin (CTb). Double-immunocytochemical characterization of the retrogradely labeled neurons is also performed. The functional significance of the identified circuits is investigated using behavioural paradigms and pharmacogenetics.

• **Methodologies Used :**

Olfactory receptor expression in heterologous systems and functional assays
Electrophysiology (patch-clamp, EOG)
Transgenic mice
Intact epithelium preparation
Connectomics using PRV viruses
Pharmacogenetics
Basic behavioral tests

Publications

Cadiou H, Aoudé I, Tazir B, Molinas A, Fenech C, Meunier N, Grosmaitre X (2014). Postnatal odorant exposure induces peripheral olfactory plasticity at the cellular level., The Journal of neuroscience : the official journal of the Society for Neuroscience. 34(14), 4857-70

Connelly, T., Y. Yu, X. Grosmaitre, J. Wang, L.C. Santarelli, A. Savigner, X. Qiao, Z. Wang, D.R. Storm, and M. Ma (2015). G protein-coupled odorant receptors underlie mechanosensitivity in mammalian olfactory sensory neurons., PNAS. 112(2), 590

Rivière, S., V. Soubeyre, D. Jarriault, A. Molinas, E. Léger-Charnay, L. Desmoulins, D. Grebert, N. Meunier, and X. Grosmaitre (2016). High fructose diet inducing diabetes rapidly impacts olfactory epithelium and behavior in mice., Scientific Reports. (), 34011

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Movahedi, K., X. Grosmaitre, and P. Feinstein (2016). Odorant receptors can mediate axonal identity and gene choice via cAMP-independent mechanisms., Open Biology. 6(7), 160018

Tazir, B., M. Khan, P. Mombaerts, and X. Grosmaitre (2016). The extremely broad odorant response profile of mouse olfactory sensory neurons expressing the odorant receptor MOR256-17 includes trace amine-associated receptor ligands., European Journal of Neuroscience. 43(5), 608

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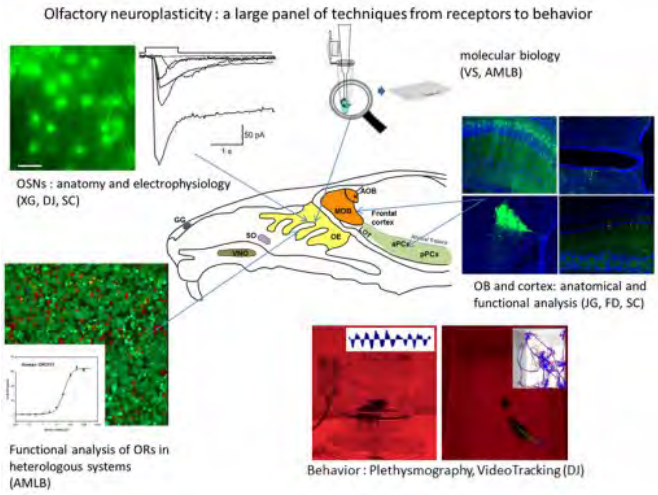
Methodological strategy developped in our group



Investigation of olfactory neuroplasticity from olfactory receptors to central areas of the brain and behavior.

Grosmaitre Xavier - xavier.grosmaitre@u-bourgogne. fr - +33 3 80 68 16 58 - https://www2.dijon.inra.fr/csga/site_engl/equipe_4.php

Endocrinology

Key facts

Team

- Researchers : 9
- Technicians : 2
- Postdoc fellows : 1
- PhD Students : 2

Translational approaches

- Patents : 1
- Clinical research grants : 2
- Industry partnerships : 2

Keywords

- Atherome
- endothelium
- monocytes/macrophages
- estrogen receptor
- endocrine dysruptor
- .

Jean-François Arnal

Estrogen Receptor alpha modulation to prevent atheroma and diabetes

Université de Toulouse 3
(Université Paul Sabatier)
Inserm U1048
Angelo Parini
Toulouse

> ***This in vivo understanding of the beneficial vascular and metabolic actions from the sexual actions will provide molecular rationale to pave the way to selective ER modulators and a better understanding of the mechanisms of action of endocrine dysruptors.***

Research Brief :

In the last years, we contributed to evidence that, beside the prevention of osteoporosis, targeting estrogen signalling allow to prevent the development or the progression of atherosclerosis and type II diabetes. Thanks to unique transgenic mouse models, we were the first to demonstrate that estrogen receptor ERa, but not ERb is absolutely necessary for the most of the vasculoprotective (including prevention of atheroma) and metabolic (prevention of diabetes type II) actions of E2. The dark side of estrogens is represented by their deleterious long-term action on their two main sexual targets. However, in the absence of associated progestin, the main concern is represented by the deleterious role of estrogen on uterus (endometrial proliferation) and on breast, the proliferative action favoring the risk of cancer.

The full length ERa is composed of 6 domains (from A to F) containing the 2 independent activation functions AF-1 and AF-2. Our team demonstrated recently that ERa AF-1 is not required for the vasculoprotective actions of E2, whereas it is necessary for the proliferative effects of E2 on uterus and on breast cancer cell lines.
Our goal is to further dissect in vivo, for the first time, the respective roles of ERa functions, AF-1 and AF-2 as well as the role of a fraction of ERa localized at the plasma membrane and eliciting «membrane initiated steroid signalling» to open the way to an optimization of ER modulation.

- **Methodologies Used :**

Mouse model functional exploration
mouse mutants of ERa
Large and medium scale analysis of gene expression

Publications

Billon-Gales A, Fontaine C, Filipe C, Douin-Echinard V, Fouque MJ, Flouriot G, Gourdy P, Lenfant F, Laurell H, Krust A (2009). The transactivating function 1 of estrogen receptor alpha is dispensable for the vasculoprotective actions of 17 beta-estradiol, Proc Natl Acad Sci U S A.. 106(), 2053-2058

Billon-Gales A, Krust A, Fontaine C, Abot A, Flouriot G, Toutain C, Berges H, Gadeau AP, Lenfant F, Gourdy P, Chambon P, Arnal JF (2011). Activation function 2 (af2) of estrogen receptor-{alpha} is required for the atheroprotective action of estradiol but not to accelerate endothelial healing., Proc Natl Acad Sci U S A.. 108(), 13311-13316

Abot A, Fontaine C, Buscato M, Solinhac R, Flouriot G, Fabre A, ?, Katzenellenbogen JA, Lenfant F, Greene GL, Foidart JM, Arnal JF. (2014). The uterine and vascular actions of estetrol delineate a distinctive profile of estrogen receptor alpha modulation, uncoupling nuclear and membrane activation, EMBO Mol Med.. 6(), 1328-1346

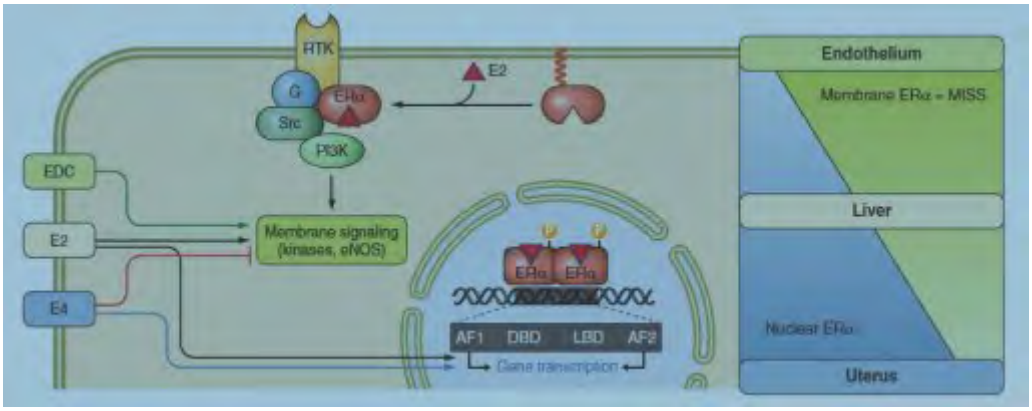
Adlanmerini M, Solinhac R, Abot A, Fabre A, Raymond-Letron I, Guihot AL, Boudou F, Sautier L, Vessieres E, Kim SH, Liere P, Fontaine C, Krust A, Chambon P, Katzenellenbogen JA, Gourdy P, Shaul PW, Henrion D, Arnal JF, Lenfant F (2014). Mutation of the palmitoylation site of estrogen receptor alpha in vivo reveals tissue-specific roles for membrane versus nuclear actions., Proc Natl Acad Sci U S A.. 111(), E283-290

Smirnova, N. F., C. Fontaine, M. Buscato, A. Lupieri, A. Vinel, M. C. Valera, M. Guillaume, ? F. Lenfant, P. Gourdy, B. S. Katzenellenbogen, J. A. Katzenellenbogen, M. Laffargue and J. F. Arnal. (2015). The Activation Function-1 of Estrogen Receptor Alpha Prevents Arterial Neointima Development Through a Direct Effect on Smooth Muscle Cells, Circ Res. 117(), 770-778

Arnal JF, Lenfant F., Métivier R, Flouriot G, Henrion D, Adlanmerini M, Fontaine C, Gourdy P, Chambon P, Katzenellenbogen BS, Katzenellenbogen JA (2017). Membrane and Nuclear Estrogen Receptor alpha actions: From Tissue Specificity to Medical Implications., Physiol. Rev.. in press(),

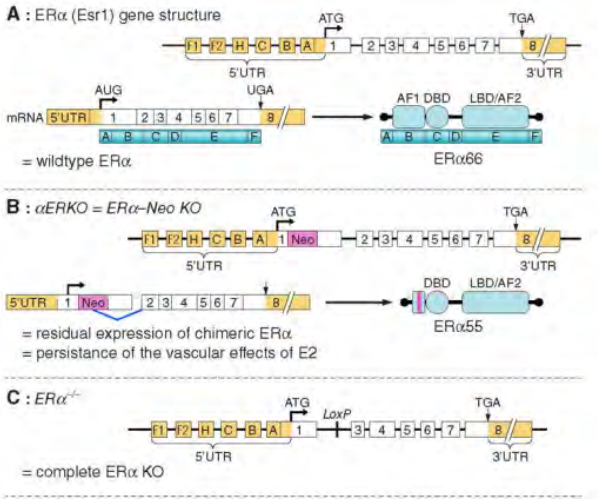
Arnal Jean-François - jean-francois.arnal@inserm.fr

Tissue specific actions of SERMs and selective usage of membrane or nuclear ERa



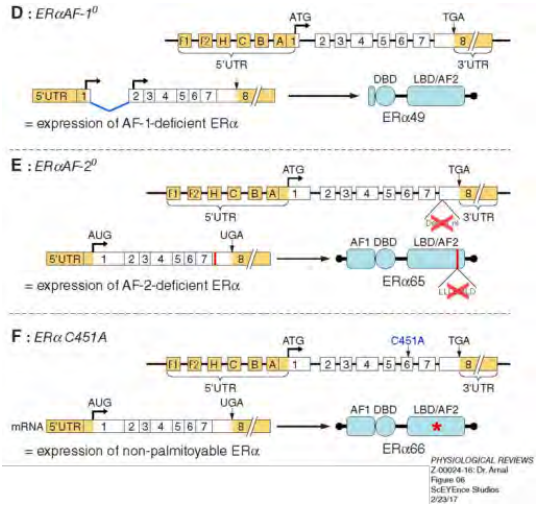
In this model, whereas E2 activates both membrane and nuclear actions of ERa, E4 (estetrol) is a weak agonist of nuclear activity and an antagonist of the ERa-dependent MISS pathways, and thereby exerts physiological actions in the uterus but not in the endothelium. EDC (estrogen dendrimer conjugate) activates only the membrane effects of ERa and thereby acts on the endothelium, but not on the uterus. The liver appears to be a mixed organ, depending on both membrane and nuclear ERa effects.

Genomic strategies for knockouts or knockins of ERa - I



(A) Schematic representation of the mouse Estrogen Receptor a (Esr1) gene, which encompasses 8 coding exons. The ERa protein is composed of six domains (A to F) comprising a DNA-binding domain (DBD), a ligand-binding domain (LBD) and two activation functions (AF-1 and AF-2).

Genomic strategies for knockouts or knockins of ERa - II



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Key facts

Team

- Researchers : 3
- Technicians : 5
- Postdoc fellows : 5
- PhD Students : 1

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 2

International research links

- Belgium
- Canada
- Italy

Keywords

- Molecular endocrinology
- Nuclear receptors
- Transcription
- Epigenetics
- Cellular biology
- Biochemistry
- Epigenetics
- Molecular biology
- Molecular pharmacology

Philippe Lefebvre

Molecular analysis of gene regulation in cardiometabolic diseases

Université de Lille
Inserm UMR1011 Institut Pasteur UMR1011
Bart Staels
Lille

A long term, proven expertise in the field of transcriptional regulation by nuclear receptors in pathology enabling the discovery of novel regulatory mechanisms and the design of new screening tools for the pharmaceutical/biotech companies

Research Brief :

Nuclear receptors (NRs) are transcription factors regulated by endocrine, lipidic or environmental (nutrients, drugs, xenobiotics) molecules which control most if not all aspects of biology, including energy homoeostasis, inflammation and cellular proliferation. These effects stem mostly from transcriptional events. Indeed, NRs are an assembly platform for distinct macromolecular complexes on DNA, whose activities concur to repress or activate transcription from a limited subset of genes by modifying the chromatin landscape in a tissue-specific manner. The impact of NR-tethered multiprotein complexes on the cellular transcriptome is conditioned by the composition of these macromolecular complexes or interactome. How this interactome varies according to physiopathological events is ill-defined, and our main research area is focusing on these aspects in cardiometabolic diseases. Using PPARgamma, a major regulator of adipocyte differentiation and of insulin sensibility, as well as FXR, the nuclear bile acid receptor, as models systems, we are characterizing the epigenetic origin of interactome variations as well as novel molecular components of this interactome that could bring selective sensitivity to pathological cues. Such a strategy will establish new paradigms to study RN-regulated transcription events which are dysregulated in metabolic diseases and which may lead to the identification of novel, original therapeutic targets.

• Methodologies Used :

Molecular biology: mutagenesis, recombinant proteins, protein-DNA interactions; protein-protein interactions, siRNA and shRNA-mediated gene knockdown
Transcriptional studies: reporter genes, Q-PCR, microarrays
Epigenetic regulation: ChIP, ChIP-Seq, RNA-Seq
Cellular Biology: Immunofluorescence, confocal microscopy, adenovirus transduction, retroviral and lentiviral transduction
Animal models: AAV-based hepatocyte transduction

Publications

Pawlak, M., Bauge, E., Bourguet, W., De Bosscher, K. Tailleux, A., Lebherz, C., Lefebvre, P. and Staels, B.* (2014). Steatosis-independent prevention of fibrosis via the anti-inflammatory activity of PPARalpha, Hepatology. 60(), 1593-1606*

Oger F, Dubois-Chevalier J, Gheeraert C, Avner S, Durand E, Froguel P, Salbert G, Staels B, Lefebvre P, Eeckhoute J (2014). Peroxisome Proliferator-activated Receptor alpha Regulates Genes Involved in Insulin/Insulin-like Growth Factor Signaling and Lipid Metabolism during Adipogenesis through Functionally Distinct Enhancer Classes., The Journal of biological chemistry. 289(), 708-22

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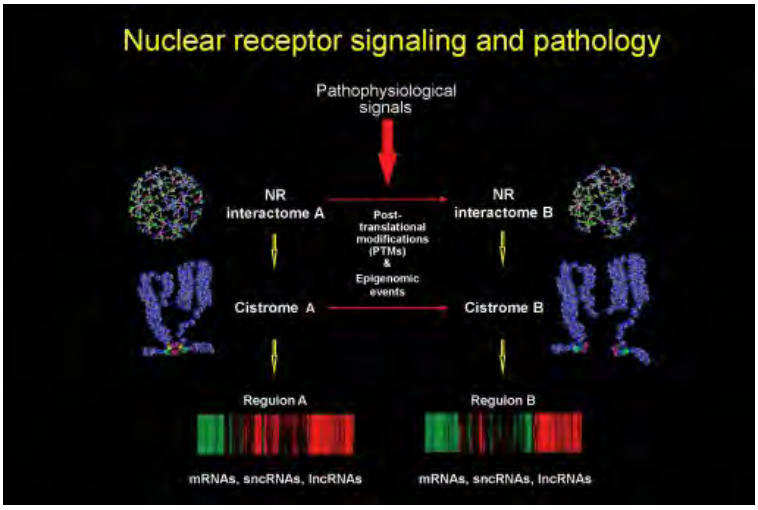
Montaigne, D.; Marechal, X.; Modine, T.; Coisne, A.; Fayad, G.; Mouton, S.; Berthier, A.; Gheeraert, C.; Potelle, C.; Debry, N.; Souissi, Z.; Alexandre, J. , Duez, H.; Koussa, M.; Edme, J.-L.; Lefebvre, P. and Staels, B. (2017). Time-of-the day and REV-ERB alpha clock gene impact myocardial ischemic tolerance., The Lancet. 391(), 59-69

Lefebvre Philippe - philippe-claude.lefebvre@inser m.fr - 03-20-97-42-20

Mechanistic investigation of nuclear receptor pathophysiology



Lefebvre Philippe - philippe-claude.lefebvre@inser m.fr - 03-20-97-42-20

Key facts

Team

- Researchers : 1
- Technicians : 1
- Postdoc fellows : 3
- PhD Students : 2

Translational approaches

- Patents : 2
- Clinical research grants : 0
- Industry partnerships : 0

Keywords

- Memory
- neuronal plasticity
- aging
- Energy balance
- Hormones
- primary hippocampal neurons
- lentiviral based gene downregulation
- stereotactic injections
- dendritic analysis
- behavioral tests

Franck Oury

Hormonal regulation of brain development and functions

Paris Descartes
Inserm U1151 CNRS UMR842
Xavier NASSIF
Paris

Hormonal regulation of brain development and cognitive functions

Research Brief :

Hormones are essential factors ensuring proper regulation of our physiological functions by mediating dialogue between organs. Their broad spectrum of actions is not limited to the peripheral organs. Some hormonal factors, such as leptin, insulin, thyroid hormones, steroid hormones reach the central nervous system (CNS) where they modulate the central regulation of whole-body metabolism. Recently, it has been shown that they can also influence more intrinsic functions of the CNS, such as brain development, adult neurogenesis and cognitive functions. Importantly, increasing evidence suggests that changes in their circulating levels may contribute to age-related cognitive decline, as well as to the development of neurodegenerative diseases.
While the functional importance of hormonal factors on brain activities is undeniable, their cellular and molecular mechanisms of action are unclear. Moreover, although the brain expresses receptors for most, if not all, hormonal factors, the role(s) of many hormones in the CNS remain unexplored. Characterizing the influence of hormonal homeostasis during aging may open up new roads for therapeutic intervention to ameliorate age- and disease-related cognitive impairments, and reverse/prevents age-related memory decline.

Methodologies Used :

We are currently using an interdisciplinary approach that combines
- mouse genetics
- behavioral/metabolic analyses
- Local brain stereotactic injections
- cellular and molecular methodologies
- lentiviral-based gene downregulation
- Hormonal measurements
- Primary neuronal cells-based assays
- Dendritic morphology and activity
- Collaborative translational studies

Publications

Oury, F., Sumara G, Sumara O, Ferron M, Chang H, Smith C.E, Hermo l, Suarez S, Roth B.L, Ducy P, Karsenty G (2011). Endocrine regulation of male fertility by skeleton, Cell. (),

Oury, F., Ferron, M., Xu, L., Confavreux, C., Srinivas, P, Lacombe, J., Wang H, Chamouni, A., Lugani, F., Lejeune, H., Kumar, TR., Plotton, I, Karsenty, G (2013). Osteocalcin regulates murine and human fertility through a pancreas-bone-testis axis, J Clin Invest. (),

Oury F, Khrimian L, Gardin A, Chamouni A, Goeden N, Huang Y, Lee H, Srinivas P, Gao XB, Suyama S, Mann JJ, Horvath T, Bonnin A, Karsenty G (2013). Maternal and offspring pools of osteocalcin influence brain development and functions, Cell. (),

Ferron M, Lacombe J, Germain A, Oury F, Karsenty G (2015). GGCX and VKORC1 inhibit osteocalcin endocrine functions, J Cell Biol. (),

Vincent Goffin

PRL/GH Pathophysiology: Translational Approaches

Université de Paris 05
(Université Paris Descartes)
Inserm U1151
Xavier Nassif
Paris

Key facts

Team

• Researchers : 3
• Technicians : 2
• Postdoc fellows : 0
• PhD Students : 1

Translational approaches

• Patents : 1
• Clinical research grants : 1
• Industry partnerships : 4

International research links

• Austria
• Australia
• USA

Keywords

• Breast and prostate cancer
• STING/IFN signaling
• Calcium signaling and nutrition
• Stem cells
• Prolactin signaling
• Gene expression studies
• Transgenic mice
• IHC
• Signaling
• In vitro cell assays
• recombinant proteins
• FACS

Biological Resources

• Recombinant proteins of the PRL/GH family (agonists, antagonists)
• Transgenic mouse models of prostate tumorigenesis (benign, malignant)

Our lab is internationally recognized for its expertise on prolactin (all aspects)

Research Brief :

We use translational approaches to identify, understand and target cellular and molecular mechanisms responsible for the progression and/or resistance to treatment of hormone-dependent cancers (breast and prostate cancers).
Aim #1. Determine the identity of castration-tolerant prostate cell(s), decipher their regulation by/downstream of PRLR signaling, and identify new actionable targets to prevent cancer relapse leading to lethal disease.
Aim #2. Elucidate the vicious circle involving calcium signaling and tissue inflammation in prostate cancer progression, in relationship with nutritional behaviors.
Aim #3. Decipher cell-autonomous IFN-related responses to treatment of breast cancer cells to develop strategies preventing/delaying cancer relapse.

• **Methodologies Used :**

- Protein engineering (production/purification of recombinant proteins, mutagenesis)
- Cell bioassays designed for basic studies and pre-clinical studies of therapeutic compounds (proliferation, reporter genes, intracellular signaling, transcriptomic profiling)
- Phenotyping of genetically-modified mouse models, focused on prostate tumors (morphology, tissue anatomy/histology, immunohistochemistry, xenografts, stem cells, gene expression)
- Clinical studies (cohorts, genotyping, immunohistochemistry)

Publications

Sackmann-Sala, L., Chiche, A., Mosquera-Garrote, N., Boutillon, F., Cordier, C., Pourmir, I., Pascual-Mathey, L., Kessal, K., Pigat, N., Camparo, P., & Goffin, V. (2014). Prolactin-Induced Prostate Tumorigenesis Links Sustained Stat5 Signaling with the Amplification of Basal/Stem Cells and Emergence of Putative Luminal Progenitors., American Journal of Pathology. 184(11), 3105

*Gaston, J., Cheradame, L., Yvonnet, V., Deas, O., Poupon, M. F., Judde, J. G., *Cairo, S., & *Goffin, V. (2016). Intracellular STING inactivation sensitizes breast cancer cells to genotoxic agents., Oncotarget. 7(47), 77205*

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*Bernichtein, S., Pigat, N., Barry Delongchamps, N., Boutillon, F., Verkarre, V., Camparo, P., Reyes-Gomez, E., Mejean, A., Oudard, S. M., Lepicard, E. M., Viltard, M., Souberbielle, J. C., Friedlander, G., *Capiod, T., & *Goffin, V. (2017). Vitamin D3 prevents calcium-induced progression of early-stage prostate tumors by counteracting TRPC6 and calcium sensing receptor upregulation, Cancer Research. 77(2), 355*

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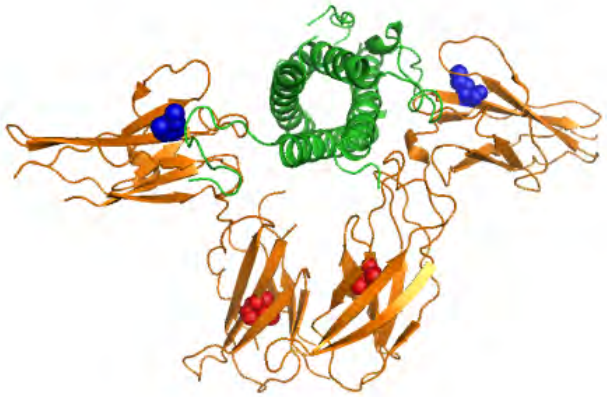
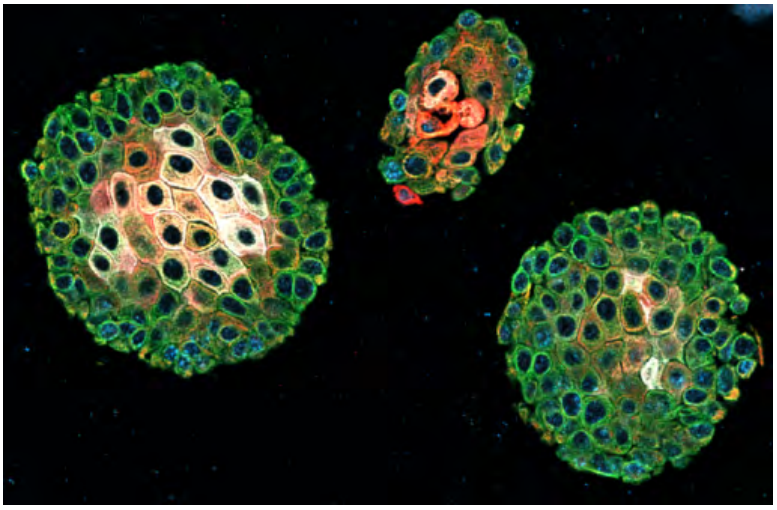
Structure of the PRL-PRL receptor complex



The crystal structure of PRL bound to its homodimerized receptor was obtained using recombinant proteins produced in the lab. On each receptor, Ile76 (blue) and Ile146 (red) are represented. Mutations of these residues confer ligand-independent receptor signaling activity. These positions correspond to natural SNPs found in the human PRL receptor.

Prostasphere generated from mouse stem cells



Sphere generation in low adherence culture media reflects the stem properties of a cell population. Each stem/progenitor cell gives rise to one sphere in which cells at various stages of differentiation can be visualized using cell-specific phenotypic markers. This figure shows prostaspheres generated after plating a population of epithelial cells dissociated from a mouse prostate. Basal cells, luminal progenitors and mature luminal cells exhibit different colors in immunoflourescence.

Key facts

Team

- Researchers : 15
- Technicians : 5
- Postdoc fellows : 0
- PhD Students : 7

Translational approaches

- Patents : 0
- Clinical research grants : 4
- Industry partnerships : 4

Keywords

- Steroid hormone signaling
- endocrinology
- human reproduction
- steroid hormone function
- imaging
- Cell Biology
- transcriptional regulation

Biological Resources

- Cellular model
- Transgenic animals

Marc Lombes

Hormone Signaling, Endocrine and Metabolic Pathophysiology

Université de Paris 11
(Université Paris Sud)
CHU Bicêtre Inserm UMR1185
Marc Lombes
KREMLIN BICETRE

Our project associating basic scientists, biologists and clinicians is entirely devoted to endocrinology and reproduction and is focused on hormone receptor signaling and their implications in human pathophysiology with therapeutic perspectives.

Research Brief :

The main projet of our Unit is devoted to translational research focused on endocrine pathophysiology and hormone signaling. The three partners of Bicêtre campus associating clinicians, biologists and basic scientists are working together to develop better understanding of molecular and cellular endocrinology.
We pursue studies on the mechanism of action of hormones by analyzing their specific receptors and their molecular partners, their implication in endocrine and metabolic pathophysiology in humans. Using complementary approaches, associating cellular and molecular biology, molecular pharmacology, integrated physiology, genetic analysis, we aim to investigate two interdisciplinary research axes:
??Nuclear receptors and transcriptional coregulators? dedicated to investigate the expression and the tissue-specific regulation of steroid receptors (mineralocorticoid, glucocorticoid, progesterone, androgens) and of their molecular coregulators, which represent key factors of hormonal responsiveness in target organs (kidney, heart, endometrium, adipose tissues, testis). We are also interested in other nuclear receptors notably xenobiotic receptor and pituitary tumorigenesis as well as adrenocortical carcinoma.
? Reproduction and hormone regulation (including prolactin and growth hormone) of the hypothalamo-pituitary-gonad axis in the context of ovary and testis dysfunction or hypogonadotropic hypogonadism associated to puberty and fertility abnormalities.

• **Methodologies Used :**

Cell biology
Transcriptional and post-transcriptional regulation
Transgenic animals
Human pathophysiology
Hormone signaling

Publications

Sonigo C, Bouilly J, Carré N, Tolle V, Caraty A, Tello J, Simony-Conesa FJ, Millar R, Young J, Binart N. (2012). Hyperprolactinemia-induced ovarian acyclicity is reversed by kisspeptin administration., J Clin Invest. 122(37), 379148-62

Kamenický P, Mazziotti G, Lombès M, Giustina A, Chanson P. (2014). Growth hormone, insulin-like growth factor-1, and the kidney: pathophysiological and clinical implications., Endocr Rev. 35(2), 234-81

Viengchareun S, Lema I, Lamribet K, Keo V, Blanchard A, Cherradi N, Lombès M. (2014). Hypertonicity Compromises Renal Mineralocorticoid Receptor Signaling through Tis11b-Mediated PostTranscriptional Control., J Am Soc Nephrol. 25(10), 2213-21

Vitellius G, Fagart J, Delemer B, Amazit L, Ramos N, Bouligand J, Billan FL, Castinetti F, Guiochon-Mantel A, Trabado S, Lombès M. (2016). Three Novel Heterozygous Point Mutations of NR3C1 causing Glucocorticoid Resistance., Hum Mutat. 37(8), 794-803

Bouilly J, Beau I, Barraud S, Bernard V, Azibi K, Fagart J, Fèvre A, Todeschini AL, Veitia RA, Beldjord C, Delemer B, Dodé C, Young J, Binart N. (2016). Identification of multiple gene mutations accounts for a new genetic architecture of primary ovarian insufficiency., J Clin Endocrinol Metab.. 101(12), 4541-4550

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Key facts

Team

- Researchers : 7
- Technicians : 3
- Postdoc fellows : 0
- PhD Students : 3

Translational approaches

- Patents : 1
- Clinical research grants : 8
- Industry partnerships : 3

International research links

- USA
- Canada
- GB

Keywords

- GHRH
- Growth
- Imprinting disorders
- Insulin-Like Growth Factors
- Nutrition-metabolism
- in vitro arcuate explant cultures
- animal experimentation
- hormone signaling
- exome sequencing
- alelespecific methylated multiplex RTQPCR

Yves Le Bouc Irene Netchine

IGF system and foetal and postnatal growth

Sorbonne Université -
Université Pierre et Marie
Curie Paris 6
INSERM UMRS 938
Yves LE BOUC
Paris

Analyses of imprinting anomalies of exceptional cohorts of foetal growth disorders : Beckwith-Wiedemann Syndrome and Silver Russell Syndrome

Research Brief :

In recent years, we have identified the epigenetic mechanisms involved in abnormal fetal growth and dissected the molecular mechanisms underlying the excessive growth observed in Beckwith-Wiedemann Syndrome, which is associated with a high risk of tumor development during childhood. In this context, our patented molecule, IGF Trap, has provided proof-of-concept for the inhibition of cancer cell proliferation, raising possibilities for treatment. We have identified the primary molecular lesion responsible for intrauterine growth retardation in Russell-Silver Syndrome, mirroring the abnormality of Beckwith-Wiedemann syndrome in the IGF2 gene region. In some cases, we have identified the genetic causes (mutation, deletion, duplication at the 2 centers of the 11p1.5 imprinted region, as well as others imprinted regions) of the epigenetic abnormalities underlying these syndromes. We have also investigated the impact of the IGF system on fetal and postnatal growth and metabolism in mice and particularly the role of the impact of nutrition, which is one of the major factors stimulating IGF-I biosynthesis, in growth and in the development of the GH hypothalamic-pituitary axis during the perinatal period. Early neonatal denutrition results in a definitive retardation of postnatal growth associated with the development of cardiometabolic diseases in adult. This is associated with a delayed axon growth of the GHRH neuron, a hypomethylation of the SRIH promoter and an insulin resistance.

- **Methodologies Used :**

Imprinting genomic analysis, Allele-specific methylated multiplex RTQPCR, exome sequencing, signaling analysis, nutritional experiments in mice, arcuate explants culture, IHC, HIS

Publications

Abi Habib W, Azzi S, Brioude F, Steunou V, Thibaud N, Das Neves C, Le Jule M, Chantot-Bastaraud S, Keren B, Lyonnet S, Michot C, Rossi M, Pasquier L, Gicquel C, Rossignol S, Le Bouc Y, Netchine I. (2014). Extensive investigation of the IGF2/H19 imprinting control region reveals novel OCT4/SOX2 binding site defects associated with specific methylation patterns in Beckwith-Wiedemann syndrome., Hum Mol Genet. 23(21), 5763-73

Rozzi FV, Koudou Y, Froment A, Le Bouc Y, Botton J. (2015). Growth pattern from birth to adulthood in African pygmies of known age, Nat Commun. 6(7672), doi: 10.1038

Decourtye L, Mire E, Clemessy M, Heurtier V, Ledent T, Robinson IC, Mollard P, Epelbaum J, Meaney MJ, Garel S, Le Bouc Y, Kappeler L. (2017). IGF-1 Induces GHRH Neuronal Axon Elongation during Early Postnatal Life in Mice, PLoS One. 12(1), e0170083

Wakeling EL, Brioude F, Lokulo-Sodipe O, O'Connell SM, Salem J, Bliek J, Canton AP, Chrzanowska KH, Davies JH, Dias RP, Dubern B, Elbracht M, Giabicani E, Grimberg A, Grønskov K, Hokken-Koelega AC, Jorge AA, Kagami M, Linglart A, Maghnie M, Mohnike K, Monk D, Moore GE, Murray PG, Ogata T, Petit IO, Russo S, Said E, Toumba M, Tümer Z, Binder G, Eggermann T, Harbison MD, Temple IK, Mackay DJ, Netchine I. (2017). Phentype-genotype and epigenotype analysis of exceptional cohorts of Beckwith-Wiedemann Syndrome and Silver Russell Syndrome GHRH neuron Axon growth in arcuate explants culture, Nat Rev Endocrinol. 13(2), 105-124

Abi Habib W, Brioude F, Edouard T, Bennett JT, Lienhardt-Roussie A, Tixier F, Salem J, Yuen T, Azzi S, Le Bouc Y, Harbison MD, Netchine I (2018). .Genetic disruption of the oncogenic HMGA2-PLAG1-IGF2 pathway causes fetal growth restriction, Genet in Medicine. 20(2), 250-258

Brioude F, Kalish JM, Mussa A, Foster AC, Bliek J, Ferrero GB, Boonen SE, Cole T, Baker R, Bertoletti M, Cocchi G, Coze C, De Pellegrin M, Hussain K, Ibrahim A, Kilby MD, Krajewska-Walasek M, Kratz CP, Ladusans EJ, Lapunzina P, Le Bouc Y, Maas SM, Macdonald F, Õunap K, Peruzzi L, Rossignol S, Russo S, Shipster C, Skórka A, Tatton-Brown K, Tenorio J, Tortora C, Grønskov K, Netchine I, Hennekam RC, Prawitt D, Tümer Z, Eggermann T, Mackay DJG, Riccio A, Maher ER. (2018). Expert consensus document: Clinical and molecular diagnosis, screening and management of Beckwith-Wiedemann syndrome: an international consensus statement., Nat Rev Endocrinol. 14(4), 229-249

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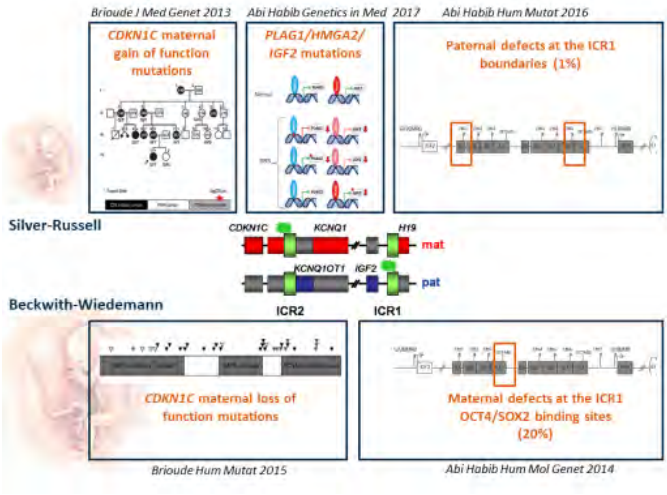
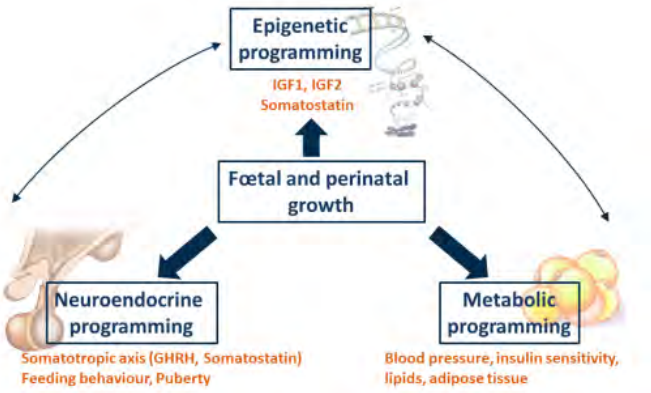
Fetal growth disorders and Imprinting abnormalities



Long term consequences of perinatal growth



Team IGF system and foetal and postnatal growth

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Key facts

Team

• Researchers : 6
• Technicians : 5
• Postdoc fellows : 2
• PhD Students : 3

Translational approaches

• Patents : 2
• Clinical research grants : 0
• Industry partnerships : 2

International research links

• Sweden, Netherlands, England,
Italy, Hungary

Keywords

• hypothalamus
• neuroendocrinology
• thyroid hormone
• adult neural stem cells
• metabolism
• germinal transgenesis
• Non viral in vivo gene transfer
• gene expression analysis

Biological Resources

• Integrated in vivo transgenic models (eg Xenopus)

Barbara Demeneix

Integration of transcriptional responses induced by thyroid hormones

Museum National d'Histoire
Naturelle
CNRS UMR7221
Giovanni Levi
Paris

The lab combines classic endocrinology with cutting edge technology (gene to organism approach to physiology with core facilities for laser microdissection, in vivo gene transfer and neurobiological technique) with a good balance between fundamental research and translational applications.

Research Brief :

Our team has the overarching objective of analysing how thyroid hormone signalling is integrated in whole body physiology during development and ageing. Our research is examining the possibility that it exists a common cellular basis for two apparently distinct areas of thyroid function : metabolism and orchestration of developmental processes. Metamorphosis in fish and anuran amphibians are striking examples of TH-dependent developmental remodelling. Metamorphosis can be seen as a parallel to mammalian postnatal development, with marked TH changes occurring in the maturing nervous system, intestine and bone. Given the links between senescence and tissue renewal capacity and the inverse correlations of TH hormone levels with longevity (see Bowers et al., 2013) we propose the hypothesis that TH availability in tissues controls metabolic responses and self-renewal and regenerative capacity. We have four main research axes:
1. To determine how changes in central, hypothalamic TH availability and action affect metabolism and longevity
2. To discover how cellular transitions in the adult neural stem cell (NSC) niche relate to local changes in TH hormone availability, gene expression, epigenetic signatures and cellular metabolism
3. To identify TH-induced changes determined during development with a potential for reversibility using the regenerating heart as a model
4. To examine how thyroid hormone signalling during development can be modulated by xenobiotics as endocrine disrupto

• **Methodologies Used :**

-Mouse and Xenopus models, ICV injections (mouse); Non-viral in vivo gene transfer (shRNA, gene overexpression, reporter genes) in mouse brain ; germinal transgenesis in Xenopus, crispr/cas9 technology in xenopus.
-Laser microdissection, In situ hybridisation; immunohistochemistry; hormone assays; gene expression analysis (qRT-PCR) ; Neurosphere culture, metabolic characterisation.
-Development of fluorescent transgenic reporter Xenopus embryos compatible with high throughput (robotised) readings (pharmaceutical screening and environmental monitoring, exploited by the SME WatchFrog).

Publications

6. Decherf S, Seugnet I, Kouidhi S, Lopez-Juarez A, Clerget-Froidevaux MS, Demeneix BA. (2010). Thyroid hormone exerts negative feedback on hypothalamic type 4 melanocortin receptor expression, Proc Natl Acad Sci USA.. 107(9), 4471-6

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4. Bowers J, Terrien J, Clerget-Froidevaux MS, Gothié JD, Rozing MP, Westendorp RG, van Heemst D, Demeneix BA. (2013). Thyroid hormone signaling and homeostasis during aging, Endocr Rev. 34(4), 556-89

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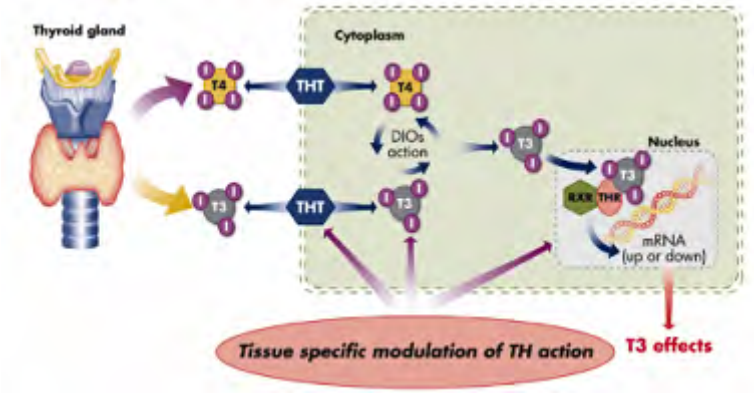
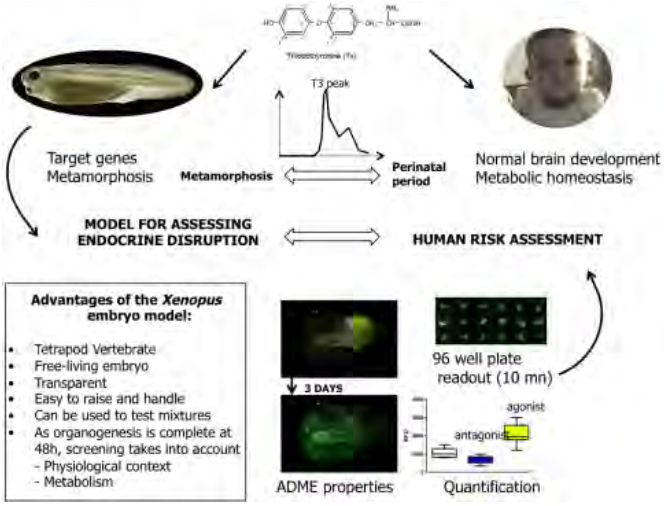
Schematic representation of cellular availability and turnover of THs



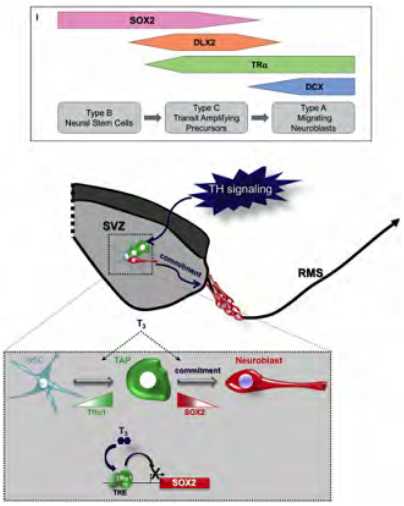
Cell-specific availability of TH is governed by transporters [THT] found at the cell membrane, and deiodinases in the cytoplasm. After release to the circulation by the thyroid gland, TH enter the cells by THTs and undergo deiodination to be activated (by D2 or D1) or inactivated (by D3 or D1). (D1 acts as an inactivating enzyme in the periphery, notably in metabolic tissues (liver)). The biologically active T3 binds to the THRs in the nucleus and activates or represses transcription.

The Xenopus Embryonic Thyroid-disruption Assay (XETA) and its pertinence to human risk assessment



XETA test principle is that the embryonic Xenopus is responsive to thyroid hormone (TH) and thus can be used to detect TH signalling disruption. TH is the same molecule in all vertebrates and many of the main elements of TH signalling are shared between vertebrates (receptors, metabolism, many target genes). Screening in Xenopus has high relevance for human toxicology. Indeed, both Xenopus and humans have key periods critically dependent on TH respectively metamorphosis and the perinatal period.

TH signaling acts as a neurogenic switch by repressing Sox2 in the adult neural stem cell niche :



In the SVZ, TR?1 is expressed in transient-amplifying cells and neuroblasts, whereas Sox2 is expressed in neural stem cells . TR?1 and SOX2 levels are inversely correlated. TR?1 overexpression in SVZ represses Sox2 and induces a DCX+ neuroblast phenotype

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Key facts

Team

• Researchers : 2
• Technicians : 0
• Postdoc fellows : 0
• PhD Students : 0

Translational approaches

• Patents : 0
• Clinical research grants : 0
• Industry partnerships : 1

International research links

• Etats Unis: The Jackson Laboratory, University of Connecticut - Yijun RUAN et Edison LIU + University of Cincinnati - Daniel BUCHHOLZ +
University of Michigan - Robert DENVER
• Chili (University of Concepcion) - Sylvain MARCELLINI
• Belgique (Université de Liège) - Mathieu DENOEL

Keywords

• thyroid hormone
• gene regulation
• functional genomic
• metamorphosis
• Epigenome
• high throughput sequencing
• bioinformatic
• in vivo gene transfert
• chromatine immunoprecipitation

Laurent Sachs

Thyroid hormone receptor function and mechanism of action

Museum Nationale d'Histoire Naturelle
CNRS UMR 7221
Giovanni Levi
Paris

The teams combines classic gene to organism approaches to physiology with core facilities for in vivo gene transfer and whole genome approaches with bioinformatics analysis of high throughput generated data.

Research Brief :

Thyroid hormones (TH) and glucocorticoids (GC) regulate diverse cellular processes from mitosis to apoptosis, from metabolism to growth and development. Perturbation of these two endocrine pathways are among the most common endocrine disorders worldwide with many consequences from early life to the elderly (mental diseases, cardiovascular diseases, metabolism associated disease, cancer, behavior and adverse effect on the quality of life). Prenatal exposure to elevated GC levels, either clinically or through maternal stress or malnutrition, can epigenetically program gene expression in the direction of previously listed diseases. The use of the Xenopus models will provide a powerful tool to understand the epigenome modification activity induced by TH and GC in whole organisms. Xenopus undergoes TH-induced metamorphosis. Interestingly, the metamorphosis and the perinatal period in mammals coincide with a peak of TH and GC. Metamorphosis thus provides a close parallel to the perinatal period. The overall aim is to identify the TH and GC induced regulatory programs operating during this key developmental phase. Such a project needs to be addressed in a physiological context and at the level of the whole genome. Thus, the ability to derive the transcriptome and a whole genome map of transcription factor binding site and their interactions as well as epigenetic modification and the enzymes that control them are crucial for elucidating gene regulatory networks.

• **Methodologies Used :**

Xenopus tropicalis model, Non viral in vivo gene transfer in brain and muscle, Germinal transgenesis in xenopus, Real time qPCR, In vivo Chromatine immunoprecipitation to dissect regulatory mechanisms and epigenetic signatures, Whole genome approach, DNA arrasy, Next generation sequencing, ChIP-Seq, ChIA-PET, MethylCAP-Seq, RNA-Seq, RNA-PET, gPET and Bioinformatics approaches.

Publications

Grimaldi A, Buisine N, Miller T, Shi Y-B, Sachs LM (2013). Mechanisms of thyroid hormone receptor action during development : Lessons from amphibian studies., Biochemica et Biophysica Acta. 1830(7), 3882-3892

Grimaldi A, Buisine N, Bilesimo P, Sachs LM (2013). High throughput sequencing will metamorphose analysis of thyroid hormone receptor during amphibian development., Current Topics in Developmental Biology. 103(), 277-303

Buisine N, Ruan X, Bilesimo P, Grimaldi A, Alfama G, Ariyaratne P, Mulawadi F, Chen J, Sung WK, Liu E, Demeneix BA, Ruan Y, Sachs LM (2015). Xenopus tropicalis genome re-scaffolding and re-annotation reach the resolution required for in vivo ChIA-PET analysis., Plos One. 10(9), e0137526

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Bronchain OJ, Chesneau A, Monsoro-Burq AH, Jolivet P, Paillard E, Scanlan TS, Demeneix BA, Sachs LS, Pollet N (SLS co-dernier) (2017). Implication of thyroid hormone signaling in neural crest cells migration: Evidence from thyroid hormone receptor beta knockdown and NH3 antagonist studies., Mol Cell Endocrinol. 439(), 233-246

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Research teams with secondary association to PMN Institute

Enzo Lalli

Mechanisms of gene expression regulation in physiopathology

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Jean-Louis Nahon
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Using an integrated approach including cell biology methods, protein structure analysis, genomics, transgenic animals and clinical studies, we aim to understand the molecular mechanisms of cancerogenesis and to develop novel therapeutic tools.

Key facts

Team

• Researchers : 3
• Technicians : 2
• Postdoc fellows : 1
• PhD Students : 1

Translational approaches

• Patents : 1
• Clinical research grants : 0
• Industry partnerships : 2

International research links

• USA
• Brazil - CNRS International Associated Laboratory "Genetics and genomics of children neoplasia" (NEOGENEX)
• Germany

Keywords

• regulation of gene expression
• cancer
• genetics
• transcription factors
• endocrinology
• mouse models
• cell biology
• molecular biology
• clinical studies
• pharmacology

Biological Resources

• Access to large Brazilian cohort of carriers of germline R337H TP53 mutation
• Adrenocortical cell lines with doxycycline-inducible SF-1 overexpression
• Transgenic mice overexpressing Sf-1 in steroidogenic tissues

Research Brief :

We aim to understand the mechanisms of gene expression in cancer, focusing on both transcriptional and post-transcriptional regulations. Particularly, in the field of adrenocortical cancer we have described the critical role of the dosage of transcription factor SF-1 in triggering tumourigenesis, characterized genomic alterations and the patterns of mRNA and miRNA deregulation, identified critically perturbed signalling pathways and demonstrated the efficacy of novel therapeutic agents in the preclinical setting.

• **Methodologies Used :**

- cell culture
- transcriptome analysis
- ChIP-seq
- transgenic mice
- protein expression in bacterial and eukaryotic systems

Publications

Doghman M, El Wakil A, Cardinaud B, Thomas E, Wang J, Zhao W, Peralta Del Valle MHC, Figueiredo BC, Zambetti GP, Lalli E (2010). Regulation of Insulin-like Growth Factor ? Mammalian Target of Rapamycin signalling by microRNA in childhood adrenocortical tumors, Cancer Research. 70(), 4666-4675

Doghman M, Figueiredo BC, Volante M, Papotti M, Lalli E (2013). Integrative analysis of SF-1 transcription factor dosage impact on genome-wide binding and gene expression regulation, Nucleic Acids Research. 41(), 8896-8907

Custódio G, Parise GA, Kiesel FN, Komechen H, Sabbaga CC, Rosati R, Grisa L, Parise IZS, Pianovski MAD, Fiori CMCM, Ledesma JA, Barbosa JRS, Figueiredo FRO, Sade ER, Ibañez H, Arram SBI, Stinghen ST, Mengarelli LR, Figueiredo MMO, Carvalho DC, Avilla SGA, Woiski TD, Poncio LC, Lima GFR, Pontarolo R, Lalli E, Zhou Y, Zambetti GP, Ribeiro RC, Figueiredo BC (2013). Impact of neonatal screening and surveillance for the TP53 R337H mutation on early detection of childhood adrenocortical tumors, Journal of Clinical Oncology. 31(), 2619-2626

Latre de Late P, El Wakil A, Jarjat M, de Krijger RR, Heckert LL, Naquet P, Lalli E (2014). Vanin-1 inactivation antagonizes the development of adrenocortical neoplasia in Sf-1 transgenic mice, Endocrinology. 155(), 4740-4748

Doghman-Bouguerra M, Granatiero V, Sbiera S, Sbiera I, Lacas-Gervais S, Brau F, Fassnacht M, Rizzuto R, Lalli E (2016). FATE1 antagonizes calcium- and drug-induced apoptosis by uncoupling ER and mitochondria, EMBO Reports. 17(), 1264-1280

Ruggiero C, Doghman-Bouguerra M, Sbiera S, Sbiera I, Parsons M, Ragazzon B, Morin A, Robidel R, Favier J, Bertherat J, Fassnacht M, Lalli E (2017). Dosage-dependent regulation of VAV2 expression by Steroidogenic Factor-1 drives adrenocortical carcinoma cell invasion, Science Signaling. 10(), eaal2464

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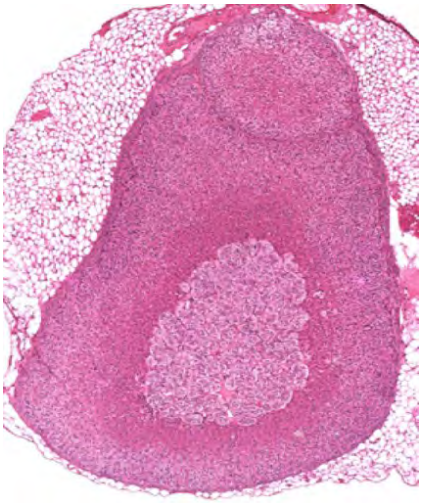
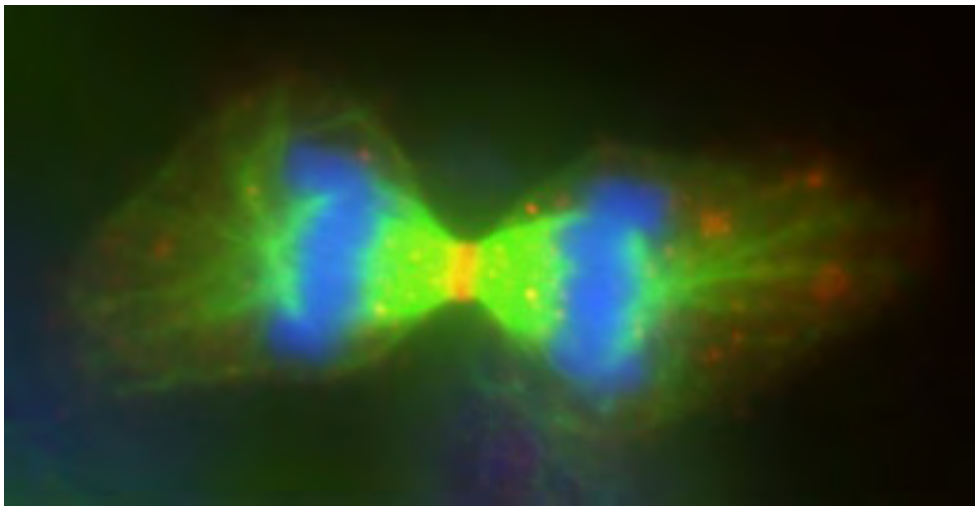
SF-1 overexpression triggers adrenocortical tumourigenesis



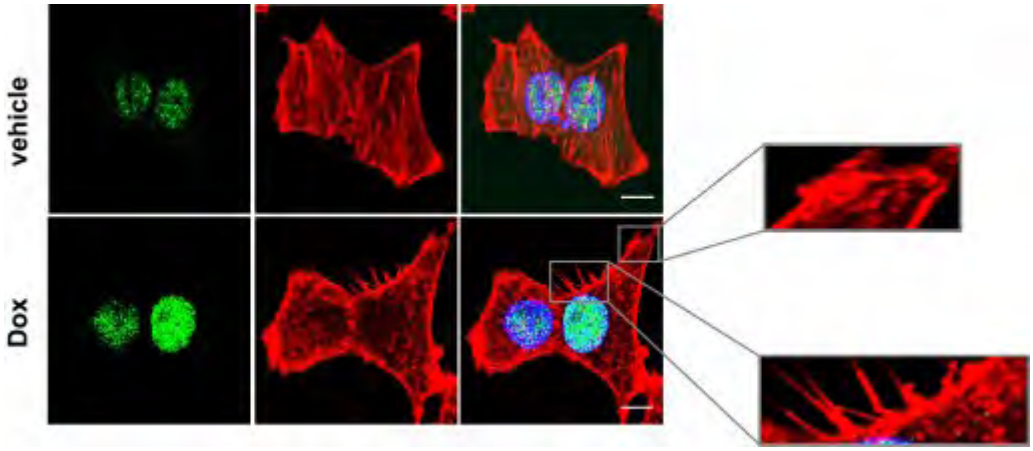
Nodule developing in the adrenal cortex of a transgenic mouse overexpressing rat Sf-1. Neoplastic cells express gonadal markers (Gata4, AMH) and are probably derived from undifferentiated adrenogonadal precursors.

Subcellular localization of phospho(Ser2448)-mTOR in mitotic adrenocortical cancer cells



The IGF-1R - mTOR pathway has a critical role in regulating proliferation of adrenocortical cancer cells. Drugs inhibiting this pathway significantly inhibit their proliferation. The specific localization of activated (Ser2448-phosphorylated) mTOR in the midbody of telophase mitotic cells suggests a role of this protein in the process of cytokinesis. Green, beta-tubulin; red, phospho(Ser2448)-mTOR; blue, DAPI staining of DNA.

Increased SF-1 dosage in adrenocortical cancer cells induces cytoskeleton remodeling



SF-1 (green) and actin cytoskeleton labeled by phalloidin (red) in H295R-TR SF-1 cells treated with either vehicle or doxycycline (Dox). SF-1 overexpression is heterogeneous in cells treated with Dox. Figure enlargements show filopodia and lamellipodia-ruffles present only in the cell with the highest SF-1 expression level.

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UMR Biologie du Developpement et Reproduction

Eric Pailhoux

DGP: Gonad Differentiation and its Perturbations

Universite Paris Saclay
INRA UMR1198
Corinne Cotinot
Jouy en Josas

Key facts

Team

- Researchers : 6
- Technicians : 4
- Postdoc fellows : 0
- PhD Students : 2

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 0

Keywords

- Sex reversal
- Gonad differentiation
- Sex determination
- Farm ruminants
- Rabbits
- Molecular biology
- Epigenetic
- Genome editing

The main originality of our team resides in the mammalian models we studied appearing quite divergent from mice according to gonadal differentiation and sexual development.

Research Brief :

The DGP team studied the genes involved in sex determination and sexual development in mammals. One of the aim of the team is to decipher the genetic pathways sustaining the main steps of gonadal differentiation (i.e.: early switch of the gonad toward testicular or ovarian development; germ cell meiosis; ovarian follicles formation; spermatogenesis) in different species of agronomical interest (mainly domestic ruminants and rabbits). Another aim of the team is to understand how these genetic pathways could be influenced by different environmental factors such as endocrine disruptors, diesel particles or maternal nutrition. The team had previously demonstrated that gonad differentiation in farm mammals used genetic pathways that differ from the widely studied mouse mammalian model.

• Methodologies Used :

As the BDR unit had a longstanding experience in reproductive biotechnologies, the team develops different strategies of additive transgenesis and, from more recently, of genome editing in domestic mammals such as goats and rabbits. By these technologies we were able to demonstrate the crucial role of the FOXL2 gene in goat ovarian differentiation; role that has been lost in the mouse model.

Publications

Daniel-Carlier N, Harscoët E, Thépot D, Auguste A, Pailhoux E, Jolivet G (2013). Gonad differentiation in the rabbit: evidence of species-specific features., PLoS One. 8(4), e60451

Boulanger L, Pannetier M, Gall L, Allais-Bonnet A, Elzaiat M, Le Bourhis D, Daniel N, Richard C, Cotinot C, Ghyselinck NB, Pailhoux E. (2014). FOXL2 is a female sex-determining gene in the goat., Current Biology. 24(4), 404-408

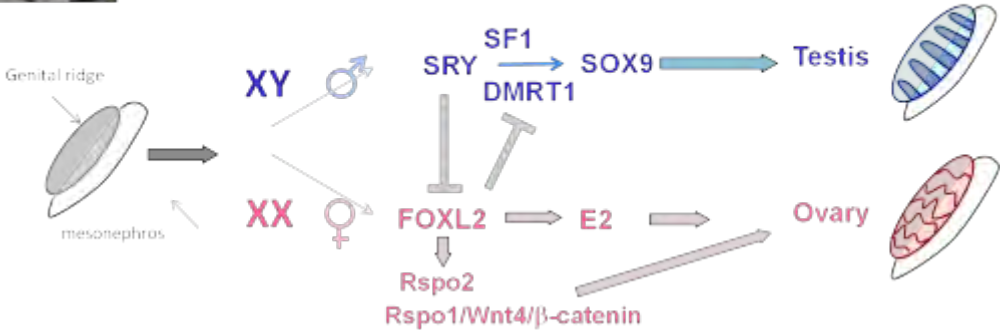
Elzaiat M, Jouneau L, Thépot D, Klopp C, Allais-Bonnet A, Cabau C, André M, Chaffaux S, Cribiu EP, Pailhoux E, Pannetier M. (2014). High-throughput sequencing analyses of XX genital ridges lacking FOXL2 reveal DMRT1 up-regulation before SOX9 expression during the sex-reversal process in goats., Biology of Reproduction. 91(6), 153

Luangpraseuth-Prosper A, Lesueur E, Jouneau L, Pailhoux E, Cotinot C, Mandon-Pépin B. (2015). TOPAZ1, a germ cell specific factor, is essential for male meiotic progression, Developmental Biology. 406(2), 158-171

Pannetier M, Chassot AA, Chaboissier MC, Pailhoux E (2016). Involvement of FOXL2 and RSPO1 in Ovarian Determination, Development, and Maintenance in Mammals., Sexual Development. 10(4), 167-184

Parma P, Veyrunes F, Pailhoux E (2016). Sex Reversal in Non-Human Placental Mammals., Sexual Development. 10(5-6), 326-344

Sex determination process in the goat species: a working model.



In goats, FOXL2 factor appears to repress the male-differentiating pathways, acting directly or not on DMRT1 gene expression. In the goat, DMRT1 may be able to promote SOX9 activation. Moreover, some clues allow the hypothesis that in addition to promoting SOX9 activation, SRY may also be involved in repressing the FOXL2gene.

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http://www6.jouy.inra.fr/bdr/Les-Recherches/Les-equipes/Differenciation-gonadique-et-ses-perturbations-DGP

Gastroenterology

André Bado

Gastrointestinal and Metabolic Dysfunctions in Nutritional Pathologies

Université de Paris 07
(Université Denis Diderot)
Inserm UMRS1149
Renato Monteiro
Paris

Our team gathers physiologists of the gastro-intestinal tract, basic scientists and clinicians (digestive surgeons, gastroenterologists and nutritionists) to develop basic and transitional researches on gastrointestinal adaptations in response to over- or under-nutrition.

Key facts

Team

- Researchers : 9
- Technicians : 0
- Postdoc fellows : 0
- PhD Students : 4

Translational approaches

- Patents : 0
- Clinical research grants : 3
- Industry partnerships : 1

International research links

- USA
- Tunisia
- Germany

Keywords

- Gastrointestinal physiology
- Leptin and Insulin
- Obesity
- Exocrine and endocrine secretions
- Nutrient transporters
- bariatric surgery and short bowel syndrome
- Transgenic mice
- Luminex
- ELISA
- FACS
- In vivo studies
- Cell culture
- IF
- Ussing chambers and transport in isolated jejunum loops
- RIA
- WB
- qPCR
- IHC

Biological Resources

- Cohorts of obese subjects before and after bariatric surgery
- Cohorts of SBS patients
- Rat models of bariatric surgery and of SBS.

Research Brief :

We focus on gastro-intestinal adaptations in response to over- or under-nutrition and gut surgeries. We set up unique rat models of bariatric surgeries - vertical sleeve gastrectomy (VSG), Roux-en-Y gastric bypass (RYGB) and one-anastomosed gastric bypass (OAGB) - and Short Bowel Syndrome (jejuno-colon or -ileum anastomosis).
Combining experimental research in these models with clinical studies, we identified differences in alimentary glucose absorption and intestinal blood glucose handling after RYGB versus VSG bariatric surgeries. We also characterized the protein malabsorption and oesophagus reflux after the controversial OAGB. Finally we characterized factors that impact on structural and functional adaptations of the remnant intestinal mucosa and microbiota in humans and rats suffering from SBS. In all those studies we highlighted the plasticity of the epithelial cells constitutive of the gastrointestinal tract.
To decipher the mechanisms of cell remodeling, we now extend our studies to either side of the epithelium: the mucosa layers containing the enteric nervous system (ENS) and immune cells versus the luminal microbiota. We want to determine the functional consequences of intestinal neuro/glio and immune cells changes and how they impact on epithelial cell functions. Finally, the metabolome of intestinal mucosa and microbiota in preclinical models and patients will allow the identification of new biomarkers and/or therapeutic targets to supply or replace surgery.

- **Methodologies Used :**

In vivo studies, Quantification of gastrointestinal secretions (endocrine, exocrine), Assay of intestinal nutrient transport, Molecular biology and pharmacology, Cell signaling, Clinical studies, Animal models of gastrointestinal weight-loss surgeries and short bowel syndrome, Transgenic mouse models

Publications

Corcos O, Cazals-Hatem D, Durand F, Kapel N, Guinhut M, Stefanescu C, Treton X, Bondjemah V, Attar A, Marmuse JP, Bouhnik Y, Joly F (2013). Intestinal failure after bariatric surgery., Lancet. 382(9893), 742

Le Beyec J, Pelletier AL, Arapis K, Hourseau M, Cluzeaud F, Descatoire V, Ducroc R, Aparicio T, Joly F, Couvelard A, Marmuse JP, Le Gall M, Bado A (2014). Overexpression of gastric leptin Precedes adipocyte leptin during high fat diet and is linked to 5HT-containing enterochromaffin cells., International journal of obesity. 144(4), 771-80

Gillard L, Billiauws L, Stan-Iuga B, Ribeiro-Parenti L, Jarry AC, Cavin JB,Cluzeaud F, Mayeur C, Thomas M, Freund JN, Lacorte JM, Le Gall M, Bado A, Joly F, Le Beyec J. (2016). Enhanced Ghrelin Levels and Hypothalamic Orexigenic AgRP and NPY Neuropeptide Expression in Models of Jejuno-Colonic Short Bowel Syndrome., Scientific Reports. (6), 26345

Cavin JB, Voitellier E, Cluzeaud F, Kapel N, Marmuse JP, Chevallier JM, Msika S, Bado A, Le Gall M. (2016). Malabsorption and intestinal adaptation after one anastomosis gastric bypass compared with Roux-en-Y gastric bypass in rats., Am J Physiol Gastrointest Liver Physiol.. 311(3), 492-500

Cavin JB, Couvelard A, Lebtahi R, Ducroc R, Arapis K, Voitellier E, Cluzeaud F, Gillard L, Hourseau M, Mikail N, Ribeiro-Parenti L, Kapel N, Marmuse JP, Bado A, Le Gall M. (2016). Differences in Alimentary Glucose Absorption and Intestinal Disposal of Blood Glucose After Roux-en-Y Gastric Bypass vs Sleeve Gastrectomy., Gastroenterology. 150(2), 454-464-1271.e1

Cavin JB, Bado A, Le Gall M. (2017). Intestinal Adaptations after Bariatric Surgery: Consequences on Glucose Homeostasis., Trends Endocrinol Metab.. 28(5), 354-364

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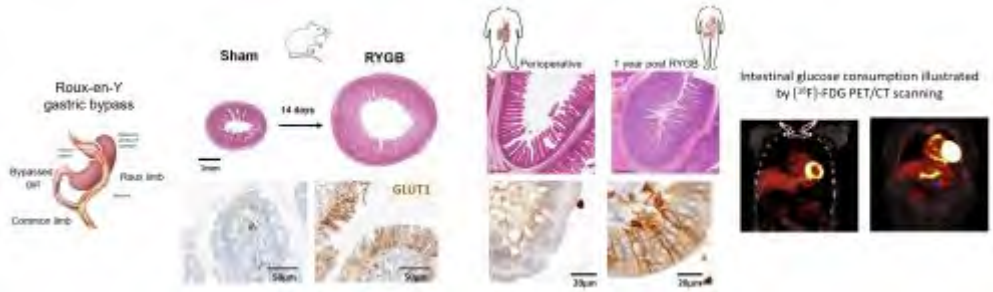
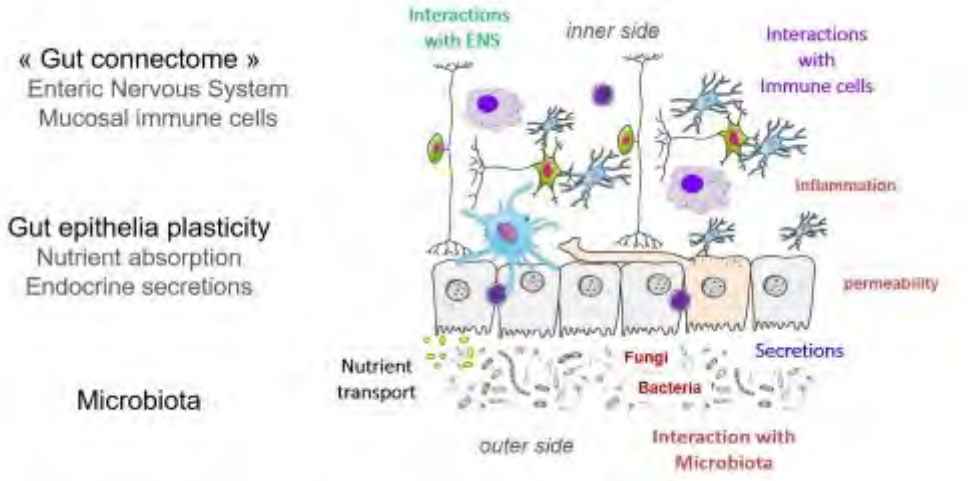
Reprogramming of intestinal glucose metabolism after gastric bypass



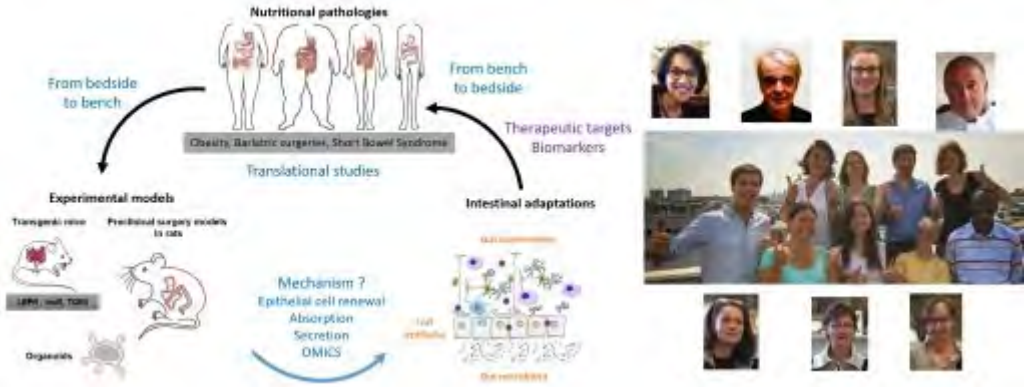
After RYGB, the jejunal mucosa in the alimentary limb becomes hyperplasic in rats, and we reported this observation in RYGB-operated obese subjects (compared to obese subjects during surgery). These hyperplasia is associated with a metabolic hyperactivity of the alimentary limb and results in increased glucose consumption, which can be visualized by PET / CT Scan analyses in humans.
Adapted from Cavin et al. Gastroenterology (2016).

Cellular and molecular mechanisms involved in the cellular plasticity of gastro-intestinal mucosa



Both sides of the gastro-intestinal epithelium could contribute to the adaptations in response to surgery readouts since glial and neurons of the enteric nervous system and immune cells communicate with epithelial cells.

Research strategies



Our team gathers physiologists of the gastro-intestinal tract, basic scientists and clinicians (digestive surgeons, gastroenterologists and nutritionists) to develop bench-to-bedsides researches.

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Key facts

Team

- Researchers : 9
- Technicians : 3
- Postdoc fellows : 1
- PhD Students : 4

Translational approaches

- Patents : 0
- Clinical research grants : 1
- Industry partnerships : 1

Keywords

- Nutrient-sensing
- GLP-1
- Intestine inflammation
- Nutrient-absorption
- Intestine barrier
- Cell culture
- Transgenic mouse
- Human jejunum
- Tissue imaging
- Hormone secretion

Biological Resources

- transgenic mouse model of nutrient detection deficiency
- cell lines
- use of jejunal samples from a cohort of obese patients (from K Clément)

Armelle Leturque

Intestine: nutrition, barrier and diseases

Université de Paris 06
(Université Pierre et Marie
Curie) Université Paris Descartes
Paris 5
Inserm UMRS_1138
Pascal Ferré
Paris

In the context of metabolic disorder epidemics, our central question focuses on the mechanisms through which intestinal cells sense environmental changes and trigger pathways required for tissue adaptation to pathophysiological situations.

Research Brief :

Major functions of intestine are to transfer nutrients to the organism, while maintaining an efficient barrier between external and internal medium, preventing the passage of antigens from bacterial or food origins, while maintaining a tolerance. Intestine, a neglected organ, has gained attention for its roles in metabolic diseases including obesity, insulin resistance, and diabetes via nutrient absorption and sensing, gut cell homeostasis and tissue inflammation.
Gathering complementary expertize in nutrition, metabolic diseases, intestine pathophysiology and epithelial intestinal cell differentiation, we aim 1-to understand how nutrients modify enteroendocrine cell lineage and function and how these changes impact pancreas, intestine and gut microbiota in obesity and diabetes; 2-to analyze the mechanisms involved in intestinal nutrient sensing via absorbing enterocytes and hormone-secreting enteroendocrine cells; 3-to decipher how signals from junctional proteins control the intestinal barrier function and trigger chronic inflammation.

- **Methodologies Used :**

Bank of jejunal samples from human obese subjects
Mouse phenotype, glucose homeostasis, food intake, blood parameters
Cell culture
Imaging in real time, in tissues sections, confocal and electron microscopy
Biochemistry, transport assays, protein expression, molecular biology constructs mutations RT-PCR transfections infections RNAi

Publications

Petit CSV, Barreau F, Besnier L, Gandille P, Riveau B, Chateau D, Roy M, Berrebi D, Svrcek M, Cardot P, Rousset M, Clair C, Thenet S (2012). Requirement of cellular prion protein for intestinal barrier function and mislocalization in patients with inflammatory bowel disease, GASTROENTEROLOGY. 143(1), 122-32

Baraille F, Ayari S, Carrière V, Osinski C, Garbin K, Blondeau B, Guillemain G, Serradas P, Rousset M, Lacasa M, Cardot P, Ribeiro A (2015). Glucose tolerance is improved in mice invalidated for the nuclear receptor HNF-4 gamma: a critical role for enteroendocrine cell lineage., DIABETES. 643(8), 2744_56

Monteiro-Sepulveda M, Touch S, Mendes-Sá C, André S, Poitou C, Allatif O, Cotillard A, Fohrer-Ting H, Hubert EL, Remark R, Genser L, Tordjman J, Garbin K, Osinski C, Sautès-Fridman C, Leturque A, Clément K, Brot-Laroche E. (2015). Jejunal T Cell Inflammation in Human Obesity Correlates with Decreased Enterocyte Insulin Signaling., CELL METABOLISM. 22(1), 113-24

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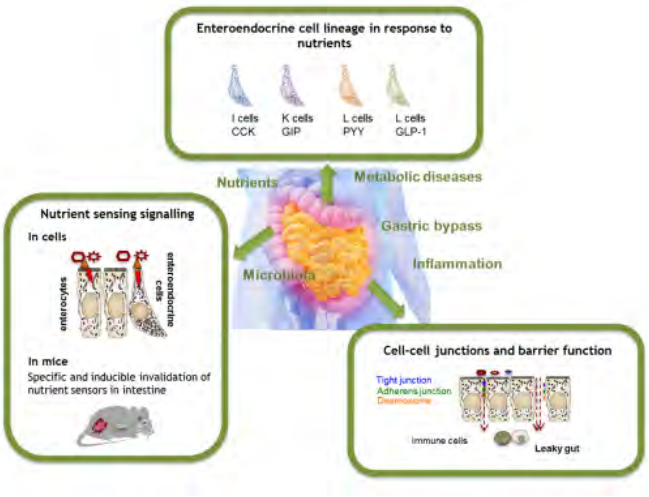
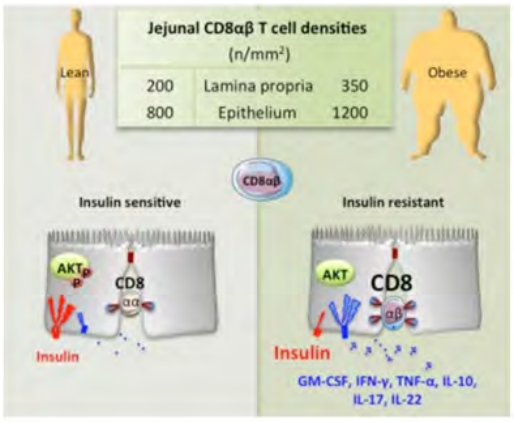
Intestine: nutrition, barrier and diseases

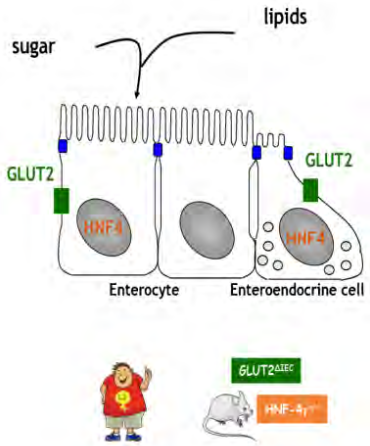


Jejunal inflammation in human obesity



Human obesity causes an increase in the jejunal mucosal surface, in both innate and adaptive immune cell densities, characterized by an increased epithelium homing of CD8 alpha beta T cells in the jejunum of obese subjects. T cells from obese subjects impair insulin sensitivity of enterocytes.(Monteiro-Sepulveda et al Cell Met 2015)

Gut nutrient sensing and enteroendocrine cell lineage



High-fat diet alters enteroendocrine L cell lineage in mice and obese subjects (Aranias et al J Nutr Sci 2015). Intestinal GLUT2 deletion induces a malabsorption, changes in gut microbiota composition and modulates L cell function (Schmitt et al Mol Met 2016). HNF4gamma deletion in mice increases L cell density and GLP-1 level leading to pancreatic islet expansion. A balance between HNF4gamma/HNF4alpha maintains glucose homeostasis and gut epithelium homeostasis (Baraille et al Diabetes 2015).

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LIRIC

Laurent Dubuquoy

Inflammatory digestive diseases: pathophysiology and development of therapeutic targets

Université du Droit et de la
Santé Lille 2
CHRU de Lille UMR995 Inserm UMR995
Pierre Desreumaux
Lille

Our strength lies in our multidisciplinary composition that promotes interactions between clinicians, scientists and surgeons, and in expertise on various tools ranging from cellular and molecular biology to animal models and histology. Access to patients allows for a unique translational approach.

Key facts

Team

- Researchers : 13
- Technicians : 5
- Postdoc fellows : 2
- PhD Students : 9

Translational approaches

- Patents : 0
- Clinical research grants : 5
- Industry partnerships : 3

International research links

- USA
- Spain
- Brasil

Keywords

- Liver
- Inflammation
- Pathophysiology
- Translational research
- Gut
- Animal models
- Microbiology
- Cellular biology
- Molecular biology
- Immunohistochemistry

Biological Resources

- Intestinal organoids
- Alcoholic liver disease biobank
- Inflammatory bowel diseases biobank
- Adherent Invasive Escherichia coli (AIEC) collection

Research Brief :

Our team is interested in the pathophysiology of inflammatory digestive diseases in order to highlight and propose new therapeutic targets for the treatment of these diseases.
A first focus on chronic inflammatory bowel disease (IBD) explores the role of nuclear receptors as well as bacterial flora in the regulation of intestinal homeostasis and is particularly interested in effector mechanisms of immunity as well as the processes involved in post-surgical recurrence.
A second focus on hepatic inflammatory diseases focuses on the pathogenesis of alcoholic hepatitis and the modulation of inflammatory liver damage by the innate immune system, while attempting to model the evolution of these diseases for the purpose to understand the impact of diagnostic methods in therapeutic decision-making.
The strength of our research team lies in its multidisciplinary composition that promotes the interaction between clinicians, scientists and industrials as well as in the expertise on various tools ranging from cellular and molecular biology techniques to animal models through histology and immunohistochemistry. Access to patient samples allows for a unique translational approach.

- **Methodologies Used :**

-Animal models of colitis (TNBS, DSS, HLAB27 Tg...), hepatitis (CCl4, ConA, Ischemia/reperfusion...)
-Cellular models of intestinal epithelium (Caco2, HT29, organoid...), Liver (hepatocyte, progenitor...) and immune cells (PMN, macrophages, lymphocytes...)
-Molecular biology (Q-PCR, plasmids, Transfection, ShRNA...)
-Histology, immunohistochemistry and imaging
-Immunology (FACS, phenotyping...)
-Microbiology (culture, metagenomic...)
-Translational approaches
-Clinical trials

Publications

Peyrin-Biroulet L, Gonzalez F, Dubuquoy L, Rousseaux C, Dubuquoy C, Decourcelle C, Saudemont A, Tachon M, Béclin E, Odou MF, Neut C, Colombel JF, Desreumaux P. (2012). Mesenteric fat as a source of C reactive protein and as a target for bacterial translocation in Crohn's disease., Gut. 61(1), 78-85

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Nieto-Bobadilla MS, Siepmann F, Djouina M, Dubuquoy L, Tesse N, Willart JF, Dubreuil L, Siepmann J, Neut C. (2015). Controlled delivery of a new broad spectrum antibacterial agent against colitis: In vitro and in vivo performance., Eur J Pharm Biopharm. 96(), 152-161

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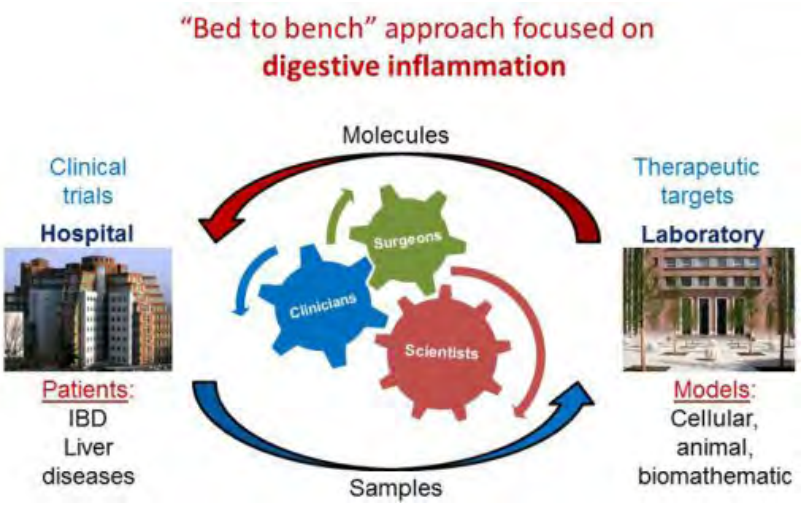
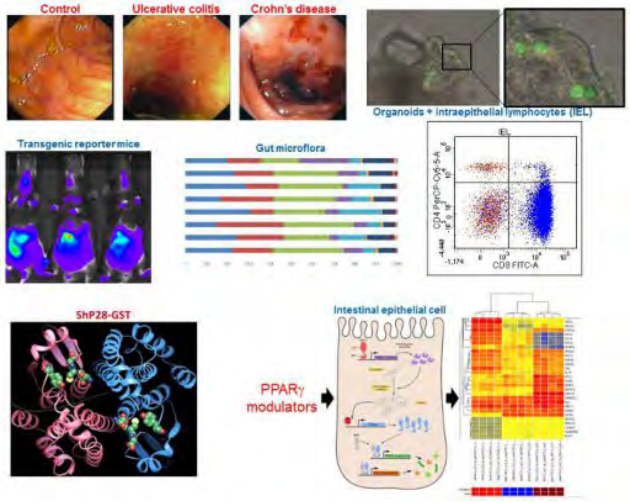
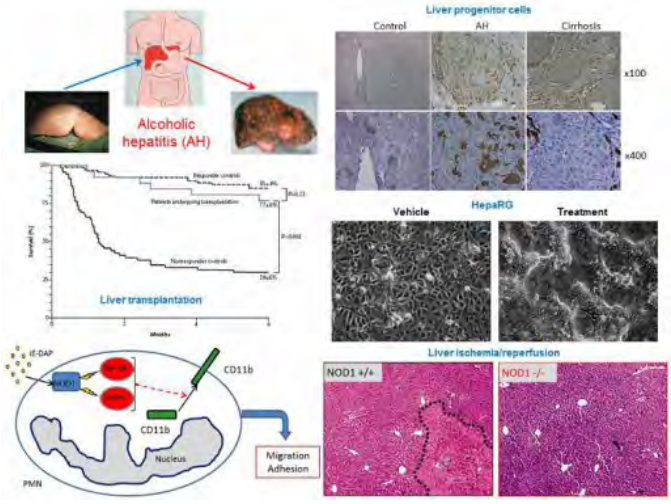
Translational research toward digestive inflammation



Inflammatory bowel diseases pathogenesis



Better understanding of liver diseases



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Nathalie Vergnolle

Pathophysiology of the intestinal epithelium

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The team, composed of nine researchers (physiologists, pharmacologists, geneticians) and one clinician gastroenterologist, has a strong expertise on several cellular actors of the intestine: epithelial cells, enteric neurons, immune cells of the lamina propria, intestinal stem cells and fibroblasts.

Key facts

Team

- Researchers : 9
- Technicians : 4
- Postdoc fellows : 3
- PhD Students : 4

Translational approaches

- Patents : 2
- Clinical research grants : 1
- Industry partnerships : 4

International research links

- Canada
- USA
- Italy

Keywords

- Inflammation
- Intestinal stem cells
- Irritable Bowel Syndrome
- Inflammatory Bowel Disease
- Pain
- 3D organoids
- Proteases
- Culture of human and murine intestinal organoids
- Primary cultures of sensory neurons (human and murine)
- In vivo models of acute and chronic colitis (DSS, TNBS, CD45RB high, IL10, etc...)
- In vivo models of somatic and visceral pain and electrography measures of pain
- In vivo and in vitro gene overexpression and silencing

Biological Resources

- Biobanks: Colonic biopsies from controls, IBS, IBD and colon cancer patients
- Human sensory neurons
- Murine neurons
- In vitro models: Colonic organoids
- Colonic epithelial cell cultures
- Measurements of PAR activatiopn in cell models

Research Brief :

We study the mediators released in chronic intestinal diseases with a focus on inflammation, infection, pain-associated pathologies and carcinogenesis. Our ultimate goal is to highlight new therapeutic targets for the treatment of intestinal diseases.
More specifically, we investigate:
- the type of proteases released by inflamed tissues and the pathophysiological effects of these proteases on epithelial barrier function, and in different other cell types involved in the inflammatory response: epithelial cells, leukocytes, monocytic cells, neurons and fibroblasts
- the mechanisms by which pathogens induce host?s protease release upon infection, and the role of proteases as mediators of host immune response
- the effects of proteases on the transmission of pain message and visceral hypersensitivity symptoms, in the context of irritable bowel syndrome and functional disorders
- the involvement of Protease Activated Receptors (PAR) in carcinogenesis pathways, their crosstalk with integrin signaling in intestinal stem cells
- the effects of the microenvironment of the colon crypts in the transition of the crypts to pre-cancerous and cancerous status, this work involves the study of immune cells, fibroblasts, but also of the enteric nervous system
- the effects of nanoparticules on epithelial barrier function and the induction of carcinogenesis
- the therapeutic potential of protease inhibitors in intestinal pathologies

- **Methodologies Used :**

- Culture of human and murine intestinal organoids
- Primary cultures of sensory neurons (human and murine)
- Co-culture systems of host epithelial cells and pathogens
- in vivo models of acute and chronic colitis (DSS, TNBS, CD45RB high, IL10, etc...)
- in vivo models of somatic and visceral pain and electrography measures of pain
- In vivo and in vitro gene overexpression and silencing
- Intestinal stem cell isolation
- Ussing chambers
- Protease identification and characterization
- Protease-Activated receptor pharmacology
- mRNA and protein expression studies
- Immunohistochemistry
- In vitro recombinant protein production

Publications

Motta, J.P., Magne, L., Descamps, D., Rolland, C., Squarzoni-Dale, C., Rousset, P., Martin, L., Cenac N., Balloy, V., Huerre, M., Jenne, D., Wartelle, J., Belaaouaj, A., Mas, E., Vinel J.P., Alric, L., Chignard, M., Vergnolle, N. & Sallenave J.M. (2011). Modifying the protease/anti-protease expression pattern by elafin over-expression protects mice from colitis, Gastroenterology. (),

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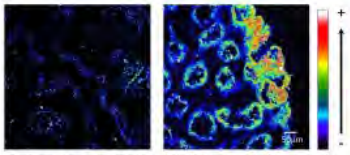
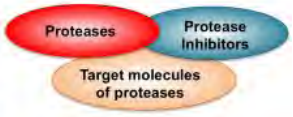
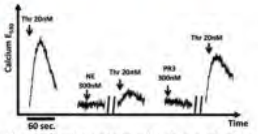
Axis 1 « Understand the role of proteolytic homeostasis in the gut »

1- Identification of proteases and protease inhibitors present in pathologies
2- Study of the role of proteolytic actors in intestinal pathologies
3- Role of proteolytic actors in epithelial cell-neighboured cell interactions
4- Therapeutic intervention



in situ zymography of proteolytic (here, elastolytic) activity in human intestinal tissues from healthy controls (CTR) and Crohn's disease (CD) patients. The intensity of colors is representative of the intensity of proteolytic activity.

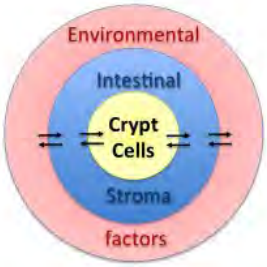




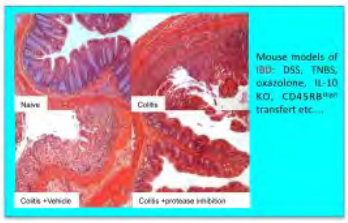
Traces showing cytoplasmic calcium release in response to Protease-Activated Receptor cleavage by active proteases

Axis 2 « Intestinal Stem Cells »

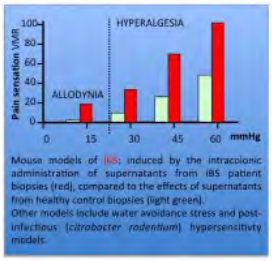
1- Identification of cellular and molecular events involved in colon tumor initiation
2- Understanding the impact of (micro)environmental alterations on the crypt cells
3- Identification of new colorectal cancer biomarkers and therapeutic targets



Axis 3 « Models of intestinal pathologies »

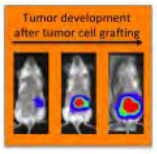


Mouse models of IBD: DSS, TNBS, oxazolone, IL-10 KO, CD45RB^{High} transfert etc....



Mouse models of IBS induced by the intracolonic administration of supernatants from IBS patient biopsies (red), compared to the effects of supernatants from healthy control biopsies (light green).
Other models include water avoidance stress and post-infectious (*citrobacter rodentium*) hypersensitivity models.

Develop 3D cultures of human colon "organoids" that mimics molecular and cellular *in vivo* complexity to test therapeutic approaches.



Key facts

Team

- Researchers : 3
- Technicians : 1
- Postdoc fellows : 0
- PhD Students : 2

Translational approaches

- Patents : 2
- Clinical research grants : 0
- Industry partnerships : 2

International research links

- Canada
- UK
- Belgium

Keywords

- Gut to brain axis
- Functional gastrointestinal disorders
- Intestinal microbiota
- Diabetes
- Intestinal inflammatory diseases
- Primary cell culture (DRG neurons, lymphocytes, monocytes, dendritic cells..)
- Tissue- and microbial-derived lipids
- Real-time measurement of reactive oxygen and nitrogen species
- Intestinal contraction (telemetry, isotonic)
- Pharmacology

Biological Resources

- Animal models of colitis
- Animal models of visceral pain
- Animal models of metabolic disorders

Gilles Dietrich

Intestinal neuro-immune interactions

Université Paul Sabatier
Toulouse III
Inserm U1220
Nathalie Vergnolle
Toulouse

The team, composed of 2 researchers and a professor of University, has a strong expertise on the enteric nervous system and intestinal mediators (hormones, neuropeptides, cytokines, bioactive lipids ...) originating from both host's cells (epithelial, nervous and immune cells) and microbiota.

Research Brief :

Intestinal inflammation often results in abdominal pain, intestinal hypercontractility and metabolism alterations including chronic hyperglycemia. Our research group in neuro-gastroenterology primarily aims at deciphering the endogenous mechanisms of regulation of visceral pain and digestive functions in the context of intestinal inflammation including endocrine and metabolic disorders such as obesity and diabetes.
Our research aims at:
- Identifying lipid compounds produced by the intestinal flora and involved in the regulation of pain and intestinal inflammation
- Better understanding the mechanisms of endogenous regulation of pain and intestinal inflammation by immune cell-derived opioids
- Better understanding the effects of intestinal mediators including immune cell-derived opioids and microbiota-derived compounds on the gut-brain axis and their consequences on glucose metabolism and insulin resistance

- **Methodologies Used :**

Primary culture (Immune cells, neurons)
Cell imaging
Cytometry (multi-staining analysis, cell sorting)
Cell biology
Molecular biology (Q RT-PCR...)
Pain measurement in vivo (visceromotor response to colorectal distention, von Frey filaments)
Identification and quantification of lipids by mass-spectrometry
Primary human/mouse sensory neuron cultures
Lipids and glucose metabolism (in vitro & in vivo)
Pharmacological studies in vitro and in vivo
Real time NO and H2O2 release in tissues in vivo and cell culture

Publications

Boue, J., Basso, L., Cenac, N., Blanpied, C., Rolli-Derkinderen, M., Neunlist, M., Vergnolle, N., and Dietrich, G (2014). Endogenous regulation of visceral pain via production of opioids by colitogenic CD4(+) T cells in mice, Gastroenterology. 146(), 166-175

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Perez-Berezo, T., Pujo, J., Martin, P., Le Faouder, P., Galano, J.M., Guy, A., Knauf, C., Tabet, J.C., Tronnet, S., Barreau, F., Heuillet, M., Dietrich, G., Bertrand-Michel, J., Durand, T., Oswald, E., Cenac, N. (2017). Identification of an analgesic lipopeptide produced by the probiotic Escherichia coli strain Nissle 1917, Nature communications. 8(), 1314

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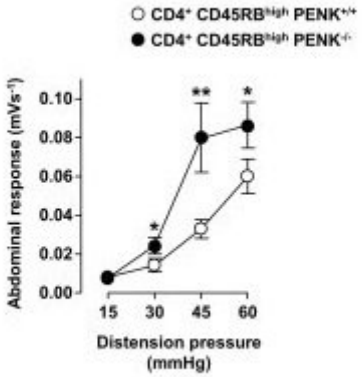
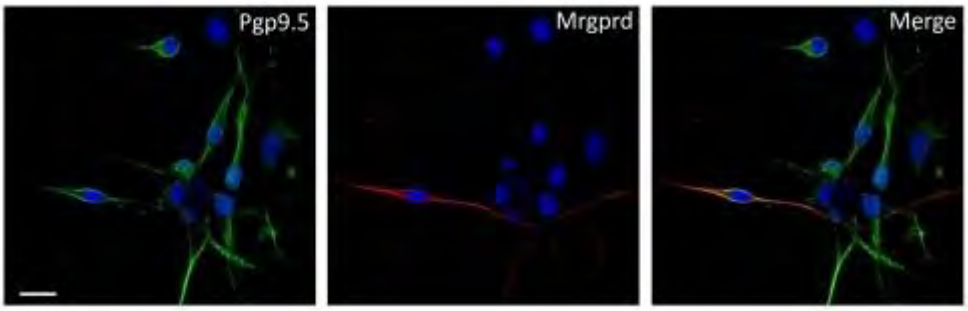
Endogenous regulation of visceral inflammatory pain by T cell-derived opioids



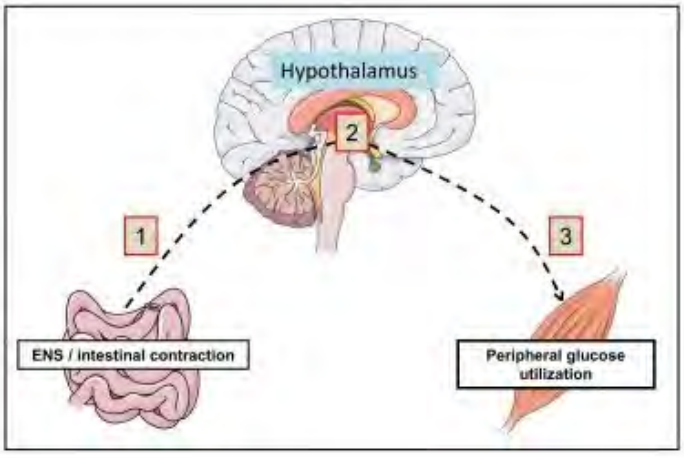
T cell-derived opioids act on mucosal immune cells and enteric nervous system (ENS) including extrinsic afferent sensory neurons (visceral pain). The figure shows colonic sensitivity to colorectal distension of RAG-2-/- mice 5 weeks after adoptive transfer of CD4+CD45RBhigh T lymphocytes from wild-type (white) or proenkephalin (PENK)-knockout mice (black). Abdominal muscle contraction was recorded in response to distension pressure of 15, 30, 45 and 60 mmHg. Data are expressed as mean ± SEM.

Fatty acids produced by the host's intestinal cells and microbiota regulate visceral pain



The long-chain fatty acid, 5-oxoETE found in colon of irritable bowel syndrome patients activates sensory neurons expressing MAS-related G protein coupled receptor D. Expression of Mrgprd (in red) in primary culture of human sensory neurons identified by the pan-neuronal marcker Pgp9.5 (in green; scale bar = 10 µm)

Impact of intestinal cells and microbiota on gut-brain axis



Modulation of ENS/duodenal contractions induces afferent signal (1) which modifies hypothalamic activity (2) and, as a result, glucose utilization in tissues (3). Intestinal motility may be modulated by a number of factors including (neuro)peptides, lipids and lipopeptides released by host's cells and/or microbiota

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Research teams with secondary association to PMN Institute

Key facts

Team

- Researchers : 9
- Technicians : 2
- Postdoc fellows : 3
- PhD Students : 2

Translational approaches

- Patents : 8
- Clinical research grants : 0
- Industry partnerships : 7

International research links

- China
- Canada
- Germany

Keywords

- Intestinal Ecosystem
- Intestinal Barrier
- Nutrition
- Gut Microbiota
- Metagenomics
- Functional metagenomics
- Metaproteomics
- HTS

Biological Resources

- Metagenomic libraries

Hervé Blottière

FInE, Funtionality of the Intestinal Ecosystem

Université Paris-Saclay
INRA UMR 1319
Stéphane Aymerich
Jouy en Josas

The FInE laboratory applies innovative metagenomics approaches to explore the functionality of the human intestinal microbial communities and study the cross-talk between gut microbiota, food and host cells.

Research Brief :

The FInE team has been the first among international laboratories to design strategies for functional exploration of genes from gut metagenomic catalogue. A platform, named MetaFun, has been created to identify bacterial genes involved in host microbiota interactions by high throughput screening. It is now part of the MetaGenoPolis project, developed in the frame of the French Investment for the Future (2012).

- **Methodologies Used :**

- Metagenomics
- Functional Metagenomics
- MetaProteomics
- Animal models

Publications

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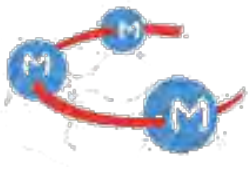
Hepatology



Philippe Gual

Chronic liver diseases associated with obesity and alcohol

Université de Nice - Sophia
Antipolis
Inserm U1065
Patrick Auberger
Nice

Key facts

Team

• Researchers : 8
• Technicians : 2
• Postdoc fellows : 0
• PhD Students : 5

Translational approaches

• Patents : 1
• Clinical research grants : 1
• Industry partnerships : 1

International research links

• EASD-NAFLD Study group

Keywords

• NAFLD, ALD, NASH, ASH, HCC
• Mice, Human

Biological Resources

• mouse model of NAFLD
• Liver, adipose tissue and serum banks of obese patients
• Cohort of obese patients
• Liver and seum banks of alcoholic patients
• Cohorts of alcoholic patients
• mouse model of ALD

Study of chronic liver diseases associated with obesity and alcohol: from the diagnosis to the treatment

Research Brief :

The aims of the present team (created in 2008), composed of clinicians and basic scientists, is to better understand the hepatic complications associated with obesity (Non alcoholic fatty liver disease: NAFLD) and with chronic alcohol consumption (alcoholic liver disease, ALD). These chronic liver diseases range from steatosis to steatohepatitis (Non Alcoholic or Alcoholic Steatohepatitis, NASH and ASH), fibrosis, cirrhosis and finally hepatocellular carcinoma.NAFLD and ALD are the main causes of cirrhosis and increase the risk of liver-related death and hepatocellular carcinoma. NASH and ALD are also the most common indications for liver transplantation in the United States.Our translational researches mainly focus on 1) the identification of new markers/actors of the progression of NAFLD and ALD. We take advantage of our cohorts of obese (n=1006) and alcoholic patients (n=173); 2) the study of potential players in the progression of NAFLD including the OPN/CD44, endoplasmic reticulum stress and ILCs pathways. The impact of targeting these pathways is investigated in mice; and 3) the study of the interaction between alcohol and obesity in the severity of fatty liver disease in mouse and human.

• **Methodologies Used :**

animal models
cellular models
human biopsies
histologic analysis
IHC
Gene and protein expression

Publications

Anty R, BekriS, Luciani N, Saint-Paul MC, Dahman M, Iannelli A, Ben Amor I, Staccini-Myx A, Huet PM, Gugenheim J, Sadoul JL, Le Marchand-Brustel Y, Tran A, Gual P (2006). The inflammatory C-reactive protein is increased in both liver and adipose tissue in severely obese patients independently from metabolic syndrome, Type 2 diabetes, and NASH., Am J Gastroenterol.. 101(8), 1824-33

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Anty R, Marjoux S, Iannelli A, Patouraux S, Schneck AS, Bonnafous S, Gire C, Amzolini A, Ben-Amor I, Saint-Paul MC, Mariné-Barjoan E, Pariente A, Gugenheim J, Gual P, Tran A. (2012). Regular coffee but not espresso drinking is protective against fibrosis in a cohort mainly composed of morbidly obese European women with NAFLD undergoing bariatric surgery., J Hepatol.. 57(5), 1090-6

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Lebeaupin C, Vallée D, Rousseau D, Patouraux S, Bonnafous S, Adam G, Luciano F, Luci C, Anty R, Iannelli A, Marchetti S, Kroemer G, Lacas-Gervais S, Tran A, Gual P, Bailly-Maitre B. (2018). Bax inhibitor-1 protects from nonalcoholic steatohepatitis by limiting inositol-requiring enzyme 1 alpha signaling in mice., Hepatology.. (Feb 19.), in press

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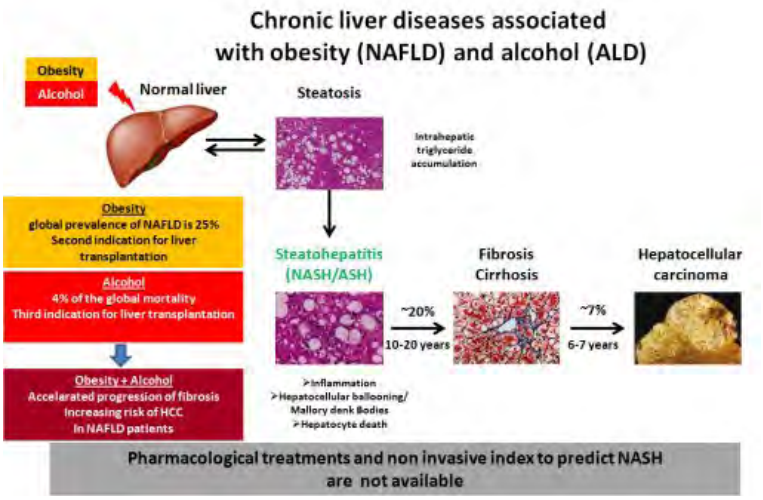
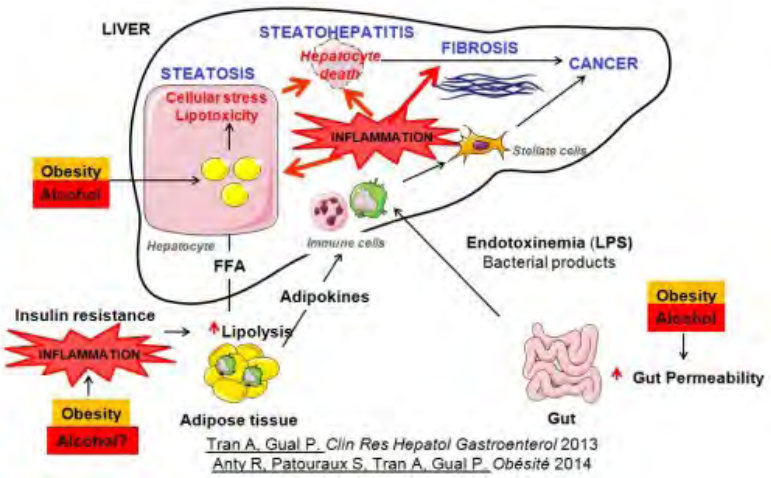
NAFLD and ALD



Obesity and regular alcohol use are associated with the development of liver diseases. The prevalence of NAFLD is 25% and up to 40% of patients with severe acute alcoholic hepatitis die within six months. The spectrum of these hepatic abnormalities extends from isolated steatosis to steatohepatitis and steatofibrosis, sometimes leading to cirrhosis and HCC. NAFLD and ALD are two of the three principal causes of cirrhosis and increase the risk of liver-related death and HCC.

Physiopathology of NAFLD AND ALD



Cross talks between the liver, adipose tissue and gut are involved in the pathogenesis of NAFLD and ALD. In obesity, increased adipose tissue inflammation leads to lipolysis and altered adipokines secretion. Obesity and alcohol consumption are associated with dysbiosis and increased gut permeability leading to elevated bacterial products. These factors enhance hepatic inflammation and hepatocyte death which initiate the fibrogenic process and the progression of liver complications

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Anne Corlu Bernard Fromenty

EXPRES

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Bruno Clément
Rennes

Key facts

Team

- Researchers : 20
- Technicians : 4
- Postdoc fellows : 2
- PhD Students : 6

Translational approaches

- Patents : 1
- Clinical research grants : 2
- Industry partnerships : 2

International research links

- Pr. Valença (Federal University of Rio de Janeiro, Brazil)
- Dr KA. Lê Cao (University of Queensland Diamantina Institute, Australia)
- Dr S. Ischida (NIHS, Tokyo, Japan)

Keywords

- Drug
- Regeneration
- Gut
- Liver
- Stress
- Cell culture
- in vivo models (mice and rats)

Biological Resources

- - Bioclinical studies in patients: cohorts of patients suffering from HCC, IBD, spina bifida and septic shock.

Our team gathers researchers and clinicians with high-level expertise in toxicology, cell defense and plasticity, metabolism and microenvironment to study the emergence and progression of metabolic and neoplastic hepatogastrointestinal diseases arising in an inflammatory context.

Research Brief :

The liver can be exposed to toxic xenobiotics, nutrient excess and inflammatory mediators released by the gastrointestinal (GI) tract. Although these tissues are able to set up mechanisms of defense and repair, the adaptive responses can be impaired in some individuals, thus favouring the occurrence of diseases such as inflammatory bowel diseases, colorectal cancer, steatohepatitis, fibrosis, cirrhosis and liver cancer. Our team aims to improve the understanding of the mechanisms involved in: i) cell and tissue damage induced by different stressors including infections and sepsis, lipid overload, surgery, hypoxia and xenobiotics, ii) cell defense and tissue repair aiming at limiting stress-induced liver and GI tract injury, iii) the occurrence of different pathological responses that can be secondary to a failure of cell defenses and tissue repair. When appropriate, we also study the impact of obesity and/or NAFLD on the response to stress and on disease progression. These objectives are included in three major research themes that are intertwined, in particular regarding cell defence, tissue repair, inflammation and mitochondrial dysfunction: 1) hepatotoxicity of xenobiotics in normal and fatty liver; 2) response to inflammatory stress and pathophysiological consequences; 3) cell plasticity in liver regeneration, fibrosis and cancer. Our project will provide new paradigms that will help to understand the pathophysiology of several important hepato-gastrointestinal diseases.

- **Methodologies Used :**

- Animal models: rat and mouse models of liver regeneration, ischemia/reperfusion, hepatocellular carcinoma (LPK-c-myc) and obesity (genetic and non-genetic)
- Cell models: primary culture of hepatocytes from human, rat or mouse liver. Cell lines (HepaRG, HepG2, Caco2, HT29?), cocultures and 3D cultures, models of steatosis and cholestasis
- Mitochondrial function (oxygraphy, SeaHorse..) and oxidative stress
- Technological platforms: Access to genomic, histopathology, microscopy, high content screening, mass-spectrometry analyses, A1 & A2 animal facilities, bio-resource center.

Publications

Massart J, Robin MA, Noury F, Fautrel A, Lettéron P, Bado A, Eliat PA, Fromenty B (2012). Pentoxifylline aggravates fatty liver in obese and diabetic ob/ob mice by increasing intestinal glucose absorption and activating hepatic lipogenesis, Br J Pharmacol. 165(1361), 1374

Dubois-Pot-Schneider H, Fekir K, Coulouarn C, Glaise D, Aninat C, Jarnouen K, Le Guével R, Kubo T, Ishida S, Morel F, Corlu A (2014). Inflammatory cytokines promote the retrodifferentiation of tumor-derived hepatocyte-like cells to progenitor cells, Hepatology. 60(2077), 2090

Bouguen G, Langlois A, Djouina M, Branche J, Koriche D, Dewaeles E, Mongy A, Auwerx J, Colombel JF, Desreumaux P, Dubuquoy L, Bertin B. (2015). Intestinal steroidogenesis controls PPARgamma expression in the colon and is impaired during ulcerative colitis., Gut. 64(901), 910

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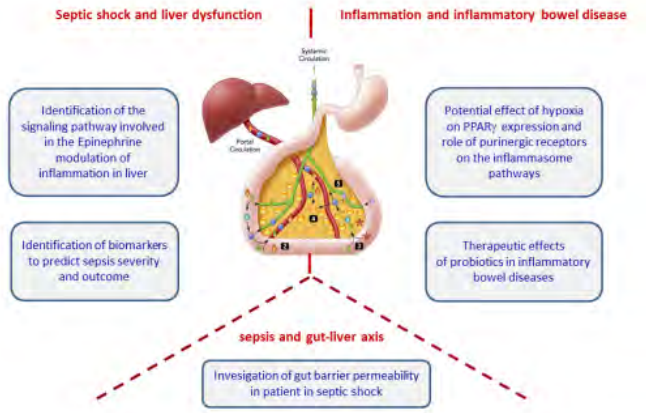
Hepatotoxicity of xenobiotics in normal and fatty liver

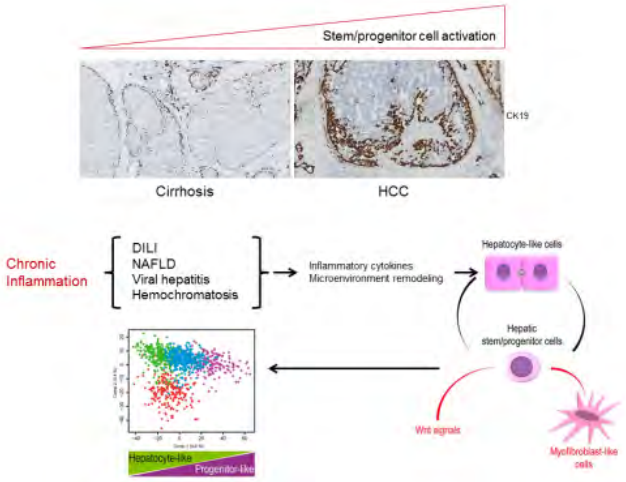
Numerous xenobiotics including drugs can lead to liver injury. Although hepatotoxicity often involves mitochondrial dysfunction and oxidative stress, several key questions remain regarding these mechanisms. Moreover, hepatotoxicity can be favoured by NAFLD, but the involved mechanisms are poorly understood. Hence, our main objectives are to further characterize the mechanisms of hepatotoxicity and to better understand why some xenobiotics are more deleterious in NAFLD and obesity.

Response to inflammatory stress and pathophysiological consequences



Several diseases (inflammatory bowel diseases, irritable bowel syndrome, sepsis,...) alter the gastrointestinal mucosa. These alterations lead to the translocation of high quantity of bacteria into the portal vein with severe pathophysiological consequences on the liver. The aim of our project is to improve the knowledge of the complex crosstalks between inflammation, hypoxia and cell defense in both gastrointestinal tract and liver in order to design new therapeutic approaches.

Cell plasticity in liver regeneration, fibrosis and cancer



Chronic liver diseases such as alcohol abuse, metabolic syndrome and viral hepatitis are characterized by recurrent bouts of liver damage and chronic inflammation resulting in fibrosis and amplification of the stem/progenitor cells. Our objectives are to study the contribution of liver inflammation to the emergence of pro-tumorigenic microenvironment, to the induction of hepatocyte plasticity and its impact on the stem/progenitor cell proliferation, metabolism and differentiation.

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Pascal Loyer Cédric Coulouarn

TGF-beta signaling, Glutathione homeostasis & innovative Therapies in Cancer (TGTC)

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Key facts

Team

• Researchers : 9
• Technicians : 3
• Postdoc fellows : 1
• PhD Students : 3

Translational approaches

• Patents : 3
• Clinical research grants : 2
• Industry partnerships : 2

International research links

• O. Coulembier (University of Mons, Belgium)
• S. Dooley (University of Heidelberg, Germany)
• R. Salem (Northwestern University, USA)

Keywords

• Metabolic radiotherapy
• TGF-beta signaling
• Vectorisation
• Glutathione homeostasis
• Liver cancer
• Genomic profiling
• In vitro cell models
• Gene and siRNA transfer
• Radioembolization
• Polymer chemistry

Biological Resources

• The head of the laboratory acting as the CSO of the national BIOBANQUES infrastructure and contributing to guidelines and recommendations for biobanking
• Approval of team projects by the national ethics committees (Inserm IRB 3888)
• Access to well-annotated human
resources and involvement in the management of the collections and CRB of Rennes

The Team gathers basic researchers and hospital practitioners with a common interest and complementary expertise in primary liver and pancreatic carcinomas to identify new therapeutic orientations for these cancers with specific emphasis on targeted therapy, vectorization and metabolic radiotherapy.

Research Brief :

The hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma and pancreatic ductal adenocarcinoma are aggressive cancers with rising incidence, poor prognosis and limited therapeutic options. Tumor onset and progression are associated with drastic changes in the tumor microenvironment promoting cancer cell survival and proliferation. The objective of the team TGTC is to better understand changes in the tumor microenvironment and their impact on tumor cell fate to provide new therapeutic orientations in cancer. We explore two paradigms, namely the TGFbeta signaling and glutathione (GSH) homeostasis. We aim at better characterizing the contextual determinants that shape the TGFbeta pathway in normal and cancer cells to provide a rationale for efficient targeted therapies using TGFbeta inhibitors. Notably, we explore the role of long non coding RNA as novel effectors and regulators of the TGFbeta pathway in cancer. We also study the contribution of the cystine/glutamate xCT antiporter in the GSH homeostasis in tumor cell fate. At the translational and clinical level, our objectives are to i) identify non-invasive companion biomarkers for targeted therapies and prognosis biomarkers (e.g. exosome content, cytokine production), ii) evaluate new clinical approaches to prevent tumor recurrence (e.g. administration of local anesthetics during surgery) and iii) develop innovative metabolic radiotherapies and synthetic nanovectors for drug delivery in HCC.

• **Methodologies Used :**

In vitro models of hepatic and pancreatic cells, establishment of recombinant cell lines, in vivo experiments in rodents, clinical trials, genomic profiling, RNA interference, RT-qPCR, protein expression and catalytic activity analysis, HPLC, phage display, formulation and cell uptake of polymeric nanoparticles, nanotoxicological evaluation, radiolabeling of microspheres.

Publications

Sulpice L, Rayar M, Desille M, Turlin B, Fautrel A, Boucher E, Llamas-Gutierrez F, Meunier B, Boudjema K, Clément B, Coulouarn C (2013). Molecular profiling of stroma identifies osteopontin as an independent predictor of poor prognosis in intrahepatic cholangiocarcinoma, Hepatology. 58(1992), 2000

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Allain C, Angenard G, Clément B, Coulouarn C (2016). Integrative Genomic Analysis Identifies the Core Transcriptional Hallmarks of Human Hepatocellular Carcinoma, Cancer Res. 76(6374), 6381

Vene E, Barouti G, Jarnouen K, Gicquel T, Rauch C, Ribault C, Guillaume SM, Cammas-Marion S, Loyer P (2016). Opsonisation of nanoparticles prepared from poly(?-hydroxybutyrate) and poly(trimethylene carbonate)-b-poly(malic acid) amphiphilic diblock copolymers: Impact on the in vitro cell uptake by primary human macrophages and HepaRG hepatoma cells, Int J Pharm. 513(438), 452

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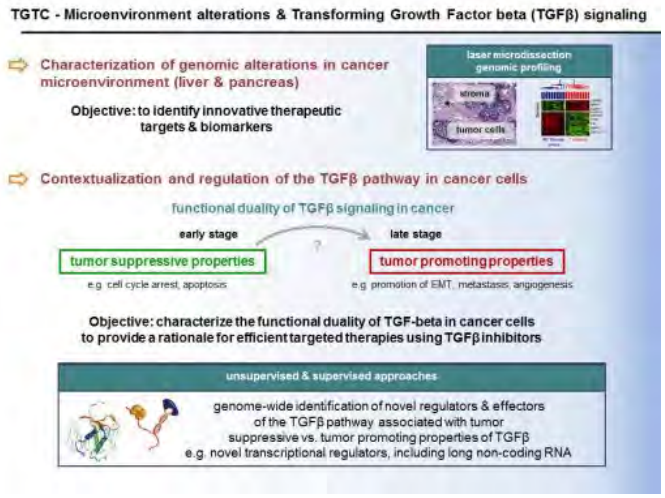
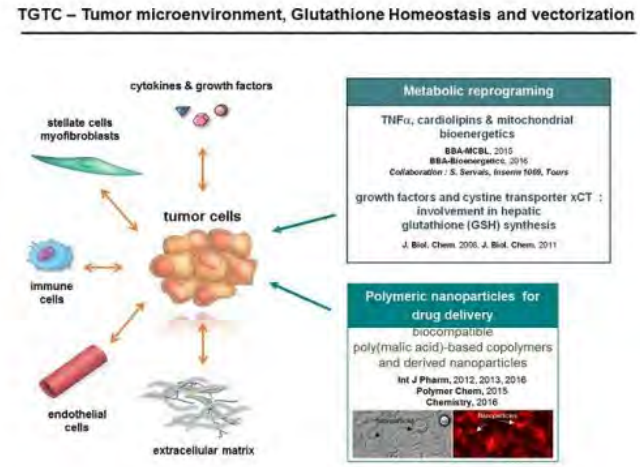
Microenvironment and TGF-beta



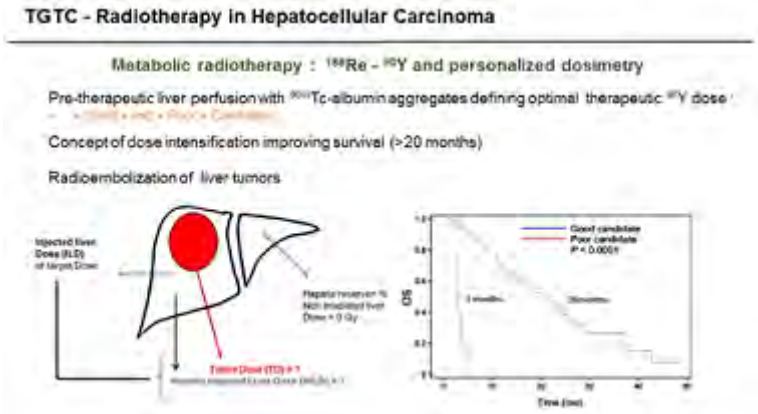
Gene profiling in liver and pancreas cancers is used to characterize genomic alterations and to identify novel therapeutic targets and biomarkers. Our objective is also to unveil new regulators and effectors of the TGFbeta pathways, including transcriptional factors and long non-coding RNA, in order to understand the functional duality of TGFbeta signaling in cancer.

Tumor microenvironment, Glutathione Homeostasis & Vectorization



Cancer progression is associated with drastic changes in the tumor microenvironment regulating signaling pathways and metabolic tumor status. We explore the contribution of the cystine/glutamate xCT antiporter in the glutathione biosynthesis and tumor cell fate. We also develop polymeric nanoparticles to target tumor cells and study the influence of the microenvironment on the nanoparticle cell uptake.

Radiotherapy in Hepatocellular Carcinoma



Our team is pioneer in the development of metabolic radiotherapy in HCC. The pre-therapeutic evaluation of 99Tc albumin aggregates accumulation led to the concept of personalized dosimetry significantly improving patient survival. We conduct clinical trials for 188Re lipiodol (phase I), 90Y microspheres (multicentric randomized phase II) and neo-adjuvant radioembolization for large tumor down-sizing.

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Key facts

Team

- Researchers : 12
- Technicians : 6
- Postdoc fellows : 2
- PhD Students : 5

Translational approaches

- Patents : 0
- Clinical research grants : 1
- Industry partnerships : 1

Keywords

- calcium signaling
- Bile acids
- Cholangiocyte
- regeneration
- cell culture
- microscopy
- molecular and cellular biology

Laurent Combettes

Cellular Interactions and Hepatic Pathophysiology

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Inserm UMRs1174
Laurent Combettes
Orsay

international recognition for our study of calcium signaling in the liver

Research Brief :

Our main objective is to determine the impact of Ca2+ signaling on the triggering and on the course of hepatocyte proliferation and regeneration, in the wide network of paracrine, endocrine and nervous interactions involved in the regulation of these processes.
We thus propose, to analyze the relationships between Ca2+ mobilizing agonists, hepatocyte calcium signalling and hepatocyte proliferation in the context of liver regeneration and carcinogenesis. Three main axes have been defined:
1-To evaluate the physiological impact of Ca2+ signaling on liver regeneration in rat and mice. We will interfere in vivo with calcium signalling before partial hepatectomy, then we will analyse consequences on regeneration.
2-To analyse the role of Sigma1 receptor, a protein involved in cell proliferation. We will focus on its role during liver regeneration and hepatocarcinogenesis in rats and human.
3-To study paracrine interactions involving calcium-mobilizing agonists, implicated during liver regeneration. We will focus on extracellular ATP, which has been shown to be involved in liver regeneration processes.
Another project of our lab is to studied PFIC2 and syndrome NISCH which are cholestases, due to mutations of BSEP (bile acids canalicular transporter) and claudin 1 (protein of tight junctions), respectively. Our aim is to understand the involved mechanisms, in order to elaborate targeted treatments and take care for the best of the affected children.

- **Methodologies Used :**

Microscopy (video, confocal, etc...)
Molecular and cellular biology
cell culture

Publications

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Peng X, Grosse B, Le Tiec B, Nicolas V, Delagebeaudeuf C, Bedda T, Decaens C, Cassio D (2006). How to induce non-polarized cells of hepatic origin to express typical hepatocyte polarity: generation of new highly polarized cell models with developed and functional bile canaliculi, CELL AND TISSUE RESEARCH. 323(2), 233-243

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Uro-Nephrology

Key facts

Team

- Researchers : 10
- Technicians : 8
- Postdoc fellows : 2
- PhD Students : 4

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 0

Keywords

- kidney; ion transport; homeostasis; pathophysiology
- electrophysiology
- microperfusion
- SAGE
- COPAS
- mathematical modeling

Biological Resources

- SAGE libraries of expression in nephron sub-segments; mouse models of renal diseases.

Aurélie Edwards Pascal Houillier

METABOLISM AND RENAL PHYSIOLOGY

Université de Paris 05
(Université Rene Descartes) Université de Paris 06
(Université Pierre et Marie
Curie)
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Paris

Our multidisciplinary team studies the mechanisms by which the kidney regulates ionic transport, adapts to its environment, and controls ionic homeostasis; our investigations span all scales, from genes to the entire organism.

Research Brief :

Our work focuses on the mechanisms of ion transport along the renal tubules, their regulation, and their dysfunction in primary or secondary renal diseases, such as hereditary tubulopathies, hypertension, and disorders of divalent cation homeostasis. We also study the cross-talk between the kidney and other tissues (gut, muscle, bone) in homeostatic regulation. Our studies integrate all scales between genes and the whole organism. The techniques we use are available through our facility for in vivo and ex vivo kidney phenotyping. Our projects have both fundamental goals and clinical objectives (e.g., identification of candidate genes/pathways in hereditary diseases, and development of new drugs). Our connections to clinical departments allow us to perform clinical investigations in patients.
Recent findings include:
*The discovery of a new pathway for sodium secretion in the aldosterone-sensitive distal nephron.
*The demonstration that basolateral ClC-K2 chloride channel may trigger HCO3- secretion by B-intercalated cells in response to alkalosis.
*The finding that nephrotic ascites formation stems from changes in capillary permeability rather than reduced plasma oncotic pressure.
*The demonstration that progesterone is a potassium-sparing hormone in both genders.
*The demonstration that the renal calcium-sensing receptor regulates calcium homeostasis.
*The discovery that MAGED2 mutation causes a new and severe form of antenatal Bartter's syndrome.

• **Methodologies Used :**

Patch-clamp, voltage-clamp;
microdissection and in vitro microperfusion of renal tubules;
in vivo analysis of kidney electrolyte balances;
SAGE analysis of transcriptomes;
mathematical modeling of renal transport.

Publications

Loupy A, Ramakrishnan SK, Wootla B, Chambrey R, de la Faille R, Bourgeois S, Bruneval P, Mandet C, Christensen EI, Faure H, Cheval L, Laghmani K, Collet C, Eladari D, Dodd RH, Ruat M, Houillier P. (2012). PTH-independent regulation of blood calcium concentration by the calcium-sensing receptor in rats., J Clin Invest. 122(9), 3355-3367

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Walters C, Ben Tanfous M, Igoudjil K, Sahli A, Escher G, and Crambert G (2016). H,K-ATPase type 2 contributes to salt-sensitive hypertension induced by K+ restriction, Pflugers Archives. 468(110), 1673-1683

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Laghmani K, Beck BB, Yang SS, et al. (2016). Polyhydramnios, Transient Antenatal Bartter's Syndrome, and MAGED2 Mutations., New England Journal of Medicine. 374(19), 1853-1863

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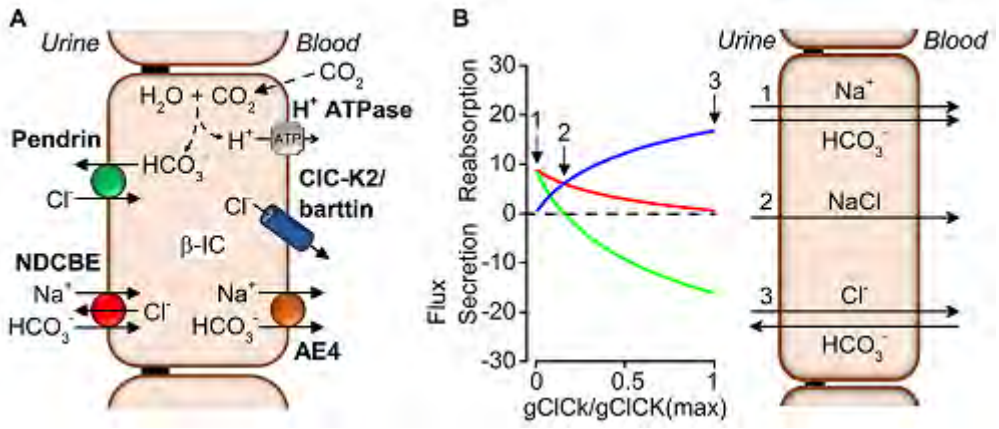
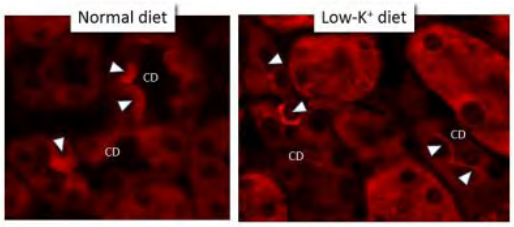
Contribution of renal CLC-K2 channels to acid-base balance.



Proposed model in which the regulation of ClC-K2 by pH provides a mechanism whereby renal beta intercalated cells can switch from primarily reabsorbing urinary Na+ with Cl- to exchanging luminal Cl- with HCO3-, thereby modulating acid?base balance (Pinelli et al, J. Gen. Physiol., 148:213-226, 2016).

Impact of K+ diet on the renal expression of H,K-ATPase type 2.



H,K-ATPase type 2 (HKA2) expression in the kidney of mice fed a normal or low K+ diet during one week. Under normal conditions, HKA2 is present in intracellular vesicles of collecting duct (CD) cells (arrows), whereas it is localized at the apical side of cells after K+ depletion.

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Key facts

Team

- Researchers : 1
- Technicians : 1
- Postdoc fellows : 1
- PhD Students : 2

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 0

International research links

- United Kingdom
- Australia
- United States

Keywords

- T cells
- dendritic cells
- endosome
- inflammation
- dendritic cells culture
- antigen presentation assays
- microscopy
- cellular biology
- mouse models

Biological Resources

- animal models with constitutive and tissues-specific IRAP deletion

Loredana Saveanu

Modulation of inflamamtory response by cell specific endosomes

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Our hallmark is the identification of insulin responsive aminopeptidase (IRAP) as a regulator of both, innate and adaptive immune response. We are intending to characterize IRAP function in immune and non-immune cells in the inflammatory reactions.

Research Brief :

Although the regulated trafficking of vesicles and their content is essential for a large diversity of cellular processes, the molecular mechanisms involved remain poorly understood. Our results from the last years indicate that the Insulin Responsive Aminopeptidase (IRAP), a type II transmembrane protein, is a dual function factor. Beside its aminopeptidase function, which is involved in antigen processing, IRAP plays an essential role in the trafficking of cell-specific storage endosomes, which is independent of its enzymatic function.
Cell-specific storage endosomes are vesicles that show a slow constitutive recycling, but can translocate rapidly to cell surface under cell-specific stimulation. Despite their broad tissues distribution, storage endosomes were initially studied almost exclusively in adipocytes, where they ensure rapid changes in surface protein composition in response to insulin stimulation. Our results on immune cells show that IRAP storage endosomes regulate the innate immunity by modulation of phagosome maturation, endosomal TLRs signaling and probably cytoskeleton remodeling. Systemic deletion of IRAP in mice generated an aberrant inflammatory response, which culminated with animal death during respiratory infections.
Based on our results obtained mainly in monocyte-derived dendritic cells, our group aims to investigate the role of IRAP storage endosomes in the inflammatory response in both immune cells (monocyte-derived dendritic cells and T cells) and

- **Methodologies Used :**

dendritic cells culture
t cell activation assays
constitutive and ko mouse models
lentiviral expression and knock-down
cell biology
confocal microscopy
TIRF microscopy
molecular biology (cloning, qRT-PCRs)
recombinant protein expression

Publications

Saveanu L, Carroll O, Weimershaus M, Guermonprez P, Firat E, Lindo V, Greer F, Davoust J, Kratzer R, Keller SR, Niedermann G, van Endert P. (2009). IRAP identifies an endosomal compartment required for MHC class I cross-presentation., Science. 325(5937), 213

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Adiko AC, Babdor J, Gutiérrez-Martínez E, Guermonprez P, Saveanu L. (2015). Intracellular Transport Routes for MHC I and Their Relevance for Antigen Cross-Presentation., Frontiers in Immunology. 2(6), 335

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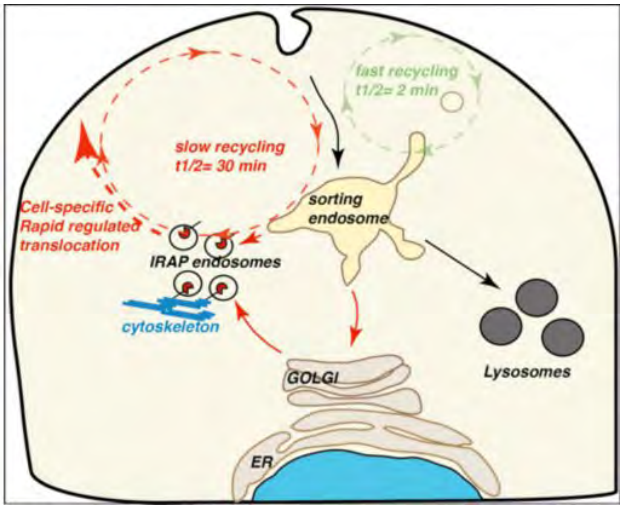
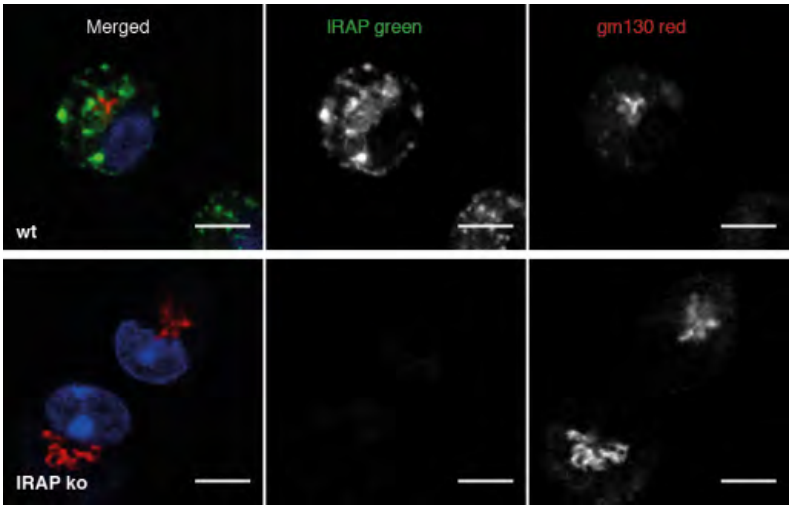
Babdor J, Descamps D, Adiko AC, Tohmé M, Maschalidi S, Evnouchidou I, Vasconcellos L, De Luca M, Mauvais FX, Garfa-Traore M, Brinkmann M, Chignard M, Manoury B, Saveanu L (2017). IRAP+ endosomes restrict TLR9 activation and signaling, Nature Immunology. on line(20), march

IRAP describes the cell specific storage endosomes



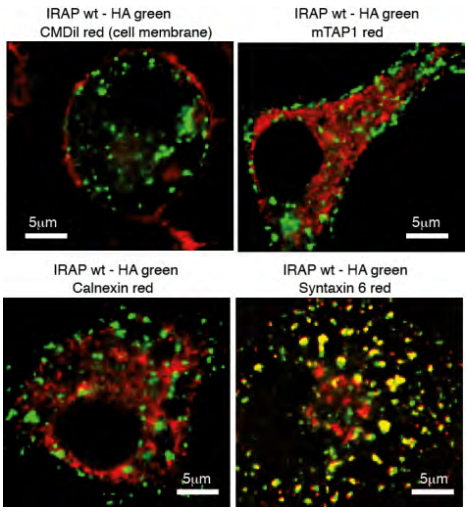
A. The aminopeptidase IRAP is the hallmark of cell-specific storage endosomes. These vesicles have a constitutive slow recycling and can be rapidly translocated to the cell surface under cell specific stimulation (insulin stimulation in adipocytes or IgE-IC in mast cells). In dendritic cells, IRAP and its endosomal compartment are involved in regulation of both, innate and adaptive immunity).

IRAP endosomes are abundant in alveolar macrophages



Alveolar macrophages were isolated from wt and IRAP deficient (IRAP ko) mice and stained with rabbit anti-IRAP (green) and mouse anti-GM130 (red) antibodies. After respiratory infection with Pseudomonas aeruginosa or influenza, IRAP deficient mice showed an increased mortality, as compared with wt mice (Babdor J, Descamps D et al., Nature Immunology 2017).

IRAP endosomes morphology (immunofluorescent microscopy) in murine dendritic cells.



Bone marrow derived dendritic cells were stained for IRAP (green) and several organelle markers (red). The Q Snare syntaxin 6 is a marker of IRAP endosoems in dendritic cells.

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Key facts

Team

- Researchers : 5
- Technicians : 3
- Postdoc fellows : 2
- PhD Students : 5

Translational approaches

- Patents : 5
- Clinical research grants : 3
- Industry partnerships : 3

Keywords

- inflammation
- neutrophil
- vasculitis
- systemic sclerosis
- apoptosis
- remodelling
- proteinase 3
- proteomic
- myeloid transfection
- cell biology

Biological Resources

- Serum, plasma, cell collections of vasculitis and systemic sclerosis patients
- DNA bank for vasculitis patients
- Collections of vascular smooth muscle cells from patients with vasculitis and collections of fibroblasts from systemic sclerosis patients
- Cohorts and data bases for systemic sclerosis and vasculitis patients
- In vitro and in vivo models of neutrophil activation and apoptosis to test pro-apoptotic anti-inflammatory molecules

Véronique Witko-Sarsat

Neutrophils and vasculitis

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The strength of the team is the synergy between basic and clinical research with an access to a large data base and unique biological material and to possess the required know-how to achieve its goals.

Research Brief :

The pathogenesis of anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitides is characterized by the involvement of neutrophils as cardinal cells that are activated and responsible for the vessel wall injury resulting in lung and renal lesions. Neutrophil activation increases expression of granule proteins such as proteinase 3 (PR3) in Wegener's granulomatosis, that are targeted by specific autoantibodies exerting pathogenic effects. Immune perturbations extend to other target cells such as endothelial cells with potential deleterious effects.
The team co-directed by Luc Mouthon is focused on the cellular and immunological aspects of vasculitis pathophysiology and takes the opportunity of the very specific recruitment of patients with systemic vasculitis of the "National reference center for systemic vasculitidis and systemic sclerosis" at Cochin Hospital.
The team has a multidisciplinary and integrative project with three aims:
1) study of the mechanisms regulating neutrophil apoptosis and their phagocytosis by macrophages, which is pivotal for the inflammation resolution and for avoiding autoimmunity
2) elucidation of the mechanisms of neutrophil activation and the role of PR3 in triggering a specific vasculitis, Wegener's granulomatosis
3) identification of target antigens and potential pathogenic role of autoantibodies against endothelial cells and vascular smooth muscle cells in vascular diseases.

• Methodologies Used :

Molecular biology, cell biology and immunochemistry techniques
Neutrophil isolation, activation and apoptosis measurement by flow cytometry
Stably transfection of myeloid cell lines, which can differentiate into mature granulocytes allow to perform loss- or gain- of function for functional studies.
Animal models of inflammation (peritonitis, vasculitis)
Proteomic analysis two dimension differential in gel electrophoresis (2D-DIGE)
Identification of target autoantigens by proteomic combined to immunoblot analysis

Publications

Witko-Sarsat V, Mocek J, Bouayad D, Tamassia N, Ribeil JA, Candalh C, Davezac N, Reuter N, Mouthon L, Hermine O, Pederzoli-Ribeil M, Cassatella MA. (2010). Proliferating cell nuclear antigen acts as a cytoplasmic platform controlling human neutrophil survival., Journal of Experimental Medicine. 207(12), 2631-45

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Proteinase 3 on apoptotic cells disrupts immune silencing in autoimmune vasculitis. Millet A, Martin KR, Bonnefoy F, Saas P, Mocek J, Alkan M, Terrier B, Kerstein A, Tamassia N, Satyanarayanan SK, Ariel A, Ribeil JA, Guillevin L, Cassatella MA, Mueller A, Thieblemont N, Lamprecht P, Mouthon L, Perruche S, Witko-Sarsat V. (2015). Proteinase 3 on apoptotic cells disrupts immune silencing in autoimmune vasculitis., Journal of Clinical Investigation. 125(11), 4107-21

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Martin KR, Kantari-Mimoun C, Yin M, Pederzoli-Ribeil M, Angelot-Delettre F, Ceroi A, Grauffel C, Benhamou M, Reuter N, Saas P, Frachet P, Boulanger CM, Witko-Sarsat V. (2016). Proteinase 3 Is a Phosphatidylserine-binding Protein That Affects the Production and Function of Microvesicles., Journal of Biological Chemistry. 291(20), 10476-89

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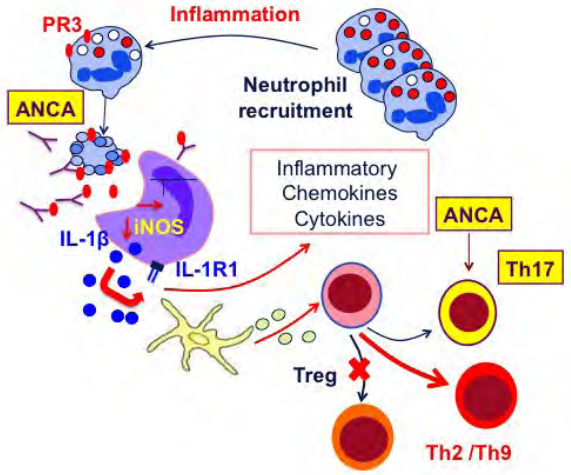
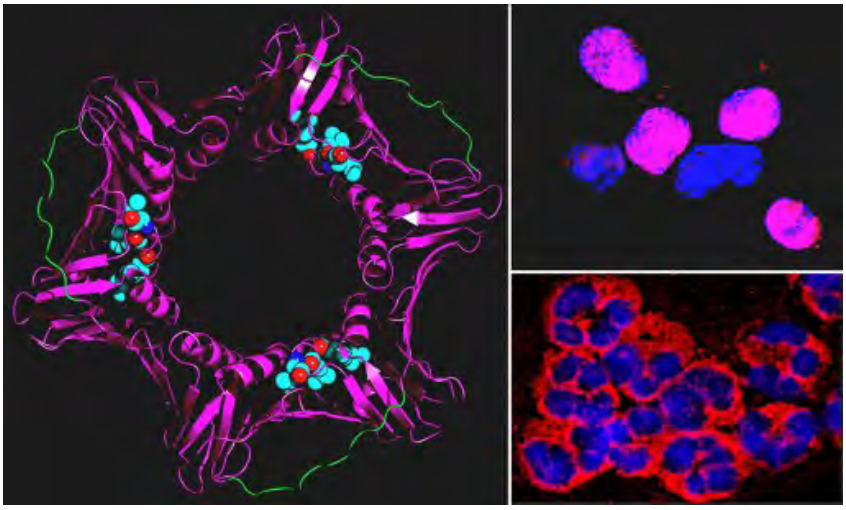
Proteinase 3, the autoantigen in vasculitis is a danger signal for the immune system.



During vascular inflammation, neutrophils can express proteinase 3 at the plasma membrane, which activates macrophages inducing the production of inflammatory cytokines. The inflammatory microenvironment favours activation of plasmacytoid dendritic cells which results in an inhibition of the generation of regulatory T cells favoring autoimmunity.

Key role of cytoplasmic PCNA in neutrophil survival



Trimeric structure of PCNA with the nuclear export sequence (NES) in blue at the inner face of the trimer. Immunofluorescence of PCNA (red) and nuclei (blue) in CD34 progenitors (upper panel). At the end of differentiation, PCNA is exported from nucleus to cytosol via its NES. In mature neutrophils, PCNA is exclusively cytosolic and is associated with different protein partners including procaspases to inhibit apoptosis (adapted from Witko-Sarsat et al J Exp Med 2010 and Immunol Reviews 2016).

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Key facts

Team

- Researchers : 15
- Technicians : 5
- Postdoc fellows : 3
- PhD Students : 5

Translational approaches

- Patents : 3
- Clinical research grants : 3
- Industry partnerships : 3

Keywords

- Renal Physiology
- Hypertension
- Renal Transplantation
- Chronic Renal Disease
- Regression of Renal Fibrosis
- Renal Hemodynamics
- Transcriptomics
- Real Time Q-PCR
- siRNA
- Intra-vital microscopy
- Renal Morphology
- Histology
- Immunocytochemistry
- Transgenic animals
- Experimental nephropathies
- Cell cultures
- stable-transient transfections

Biological Resources

- Renal cell cultures (mesangial, podocytes, vascular smooth muscle, tubular epithelial, collecting duct)
- Cohorts: Nephrotest, Corirla, European Transcriptomic Bank of Renal biopsies
- Experimental models of nephropathies that correspond to acute (ischemia-reperfusion), vascular (Ang II), glomerular (anti-GMB) and tubular (unilateral ureteral obstruction) injuries

Christos Chatziantoniou

New Biomarkers and Targets for Therapy of Chronic Kidney Disease

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These studies significantly contribute to a better understanding of the mechanisms involved in the development of renal disease and to provide important clues of how this incurable today pathology can be stopped or even better reversed

Research Brief :

The major objective of our team is to provide a comprehensive approach of mechanisms responsible for renal disease progression and repair. We are using a multi-target strategy to discover mediators of inflammation, apoptosis, initial repair, progression, stabilization or regression of renal lesions
Specific objectives are to:
- Investigate the mechanisms by which Calpains and the Discoidin Domain Receptor 1 act as major mediators of renal inflammation
- Study the importance of Notch3 to control renal autoregulation and the impact of renal vessel dysfunction in the development of renal failure
- Examine the role of cell-cell communication in the development of renal disease by focusing on Connexin 43, a protein constituting gap junctions.
- Explore the endogenous regulation of the BMP signalling pathway as opposed to TGFbeta action in mediating Epithelial to Mesenchymal Transition in renal disease.
- Search whether improving Renal Hemodynamics can protect against the progression of renal disease.
- Seek the importance of Resident Cells in renal repair
- Transfer the knowledge obtained with the experimental models to humans by analyzing the predictive value of the expression of EMT markers detected early, in 3-month protocol biopsies, on the graft function two years after transplantation

- **Methodologies Used :**

Renal Hemodynamics, BP, RBF, GFR, electrolytes
Transcriptomics, Real Time Q-PCR, siRNA,
Intra-vital microscopy, Renal Morphology, Histology, Immunocytochemistry, Transgenic animals,
Experimental nephropathies,
Cell cultures, stable-transient transfections

Publications

Vidal-Petiot E, Elvira-Matelot E, Mutig K, Soukaseum C, Baudrie V, Wu S, Cheval L, Huc E, Cambillau M, Bachmann S, Doucet A, Jeunemaitre X, Hadchouel J (2013). WNK1-related Familial Hyperkalemic Hypertension results from an increased expression of L-WNK1 specifically in the distal nephron., Proc Natl Acad Sci U S A. 110(35), 14366-71

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Luque Y, Cathelin D, Vandermeersch S, Xu X, Sohier J, Placier S, Xu-Dubois YC, Louis K, Hertig A, Bories JC, Vasseur F, Campagne F, Di Santo JP, Vosshenrich C, Rondeau E, Mesnard L. (2017). Glomerular common gamma chain confers B- and T-cell-independent protection against glomerulonephritis., JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY. in press(),

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de recherche biomédicale

Djillali Sahali

Renal immunopathology

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Créteil

Molecular pathophysiology of acquired idiopathic nephrotic syndrome

Key facts

Team

- Researchers : 9
- Technicians : 1
- Postdoc fellows : 2
- PhD Students : 4

Translational approaches

- Patents : 3
- Clinical research grants : 3
- Industry partnerships : 0

International research links

- Netherlands, Italy, USA

Keywords

- Signaling
- Lymphocyte
- Podocyte
- immune regulation
- Pathophysiology
- Gene therapy
- mouse models

Biological Resources

- DNA library
- RNA library
- Protein library
- serum library
- cohorts/biobanks
- mouse models

Research Brief :

Our work is mainly based on a bedside-to-bench project aimed to improve understanding the pathophysiology of glomerular diseases and to translate basic scientific findings into diagnostic and therapeutic perspectives for patients. The team is mainly focused on molecular pathophysiology of acquired idiopathic nephrotic syndrome (INS), including the study of both immunological and podocyte disorders. In our project, the main objectives will be: 1) to further characterize the function of a new gene, CMIP, and its role in podocyte and immunological disorders by assessing whether its deletion protects mice from experimental induction of proteinuria and by understanding the functional consequences of overexpression of CMIP in T-cell biology by targeted transgenesis and 2) to characterize new potential targets in INS recurrence recently identified in the lab. These objectives will be driven by different leaders of the team, who have established close collaboration with other teams specialized in the research field. All animal models have been generated. Financial support for these projects is provided by the reference center grant and by current and future contracts.

- **Methodologies Used :**

Subtractive and differential screening
Cloning and construction of target vectors, sequencing
SiRNA in vivo
Immunohistochemistry and confocal microscopy
Immunochemistry
Cell cultures and generation of primary cell lines
Transgenesis and conditional knock out
Proteomics (global, membrane microdomain-related and phosphoproteomics)
Lipidomics

Publications

Vincent Audard, Shao-yu Zhang, Christiane Copie-Bergman, Catherine Rucker-Martin, Virginie Ory, Marina Candelier, Maryse Baia, Philippe Lang, André Pawlak and Djillali Sahali200 (2010). Occurrence of minimal change nephrotic syndrome in classical Hodgkin lymphoma is closely related to the induction of c-mip in Hodgkin-Reed Sternberg cells and podocytes, Blood. 198(5), 797-807

Shao-yu Zhang, Maud Kamal, Karine Dahan, André Pawlak, Virginie Ory, Dominique Desvaux, Vincent Audard, Marina Candelier, Fatima Ben Mohamed, Marie Matignon, Christo Christov, Xavier Decrouy, Veronique Bernard, Gilles Mangiapan, Philippe Lang, Georges Guellaën, Pierre Ronco and Djillali Sahali (2010). c-mip Impairs Podocyte Proximal Signaling and Induces Heavy Proteinuria, Science Signaling. 13(5), 1238-1247

Virginie Ory, Qingfeng Fan, Nabila Hamdaoui, Shao-yu Zhang, Dominique Desvaux, Vincent Audard, Marina Candelier, Laure-Helene Noel, Philippe Lang, Georges Guellaën, André Pawlak and Djillali Sahali (2012). c-mip Down-Regulates NF- B Activity and Promotes Apoptosis in Podocytes, American Journal of Pathology. 172(1), 688-98

Kelhia Sendeyo1, Vincent Audard1, Shao-yu Zhang, Qingfeng Fan, Khedidja Bouachi, Mario Ollero, Catherine Rucker-Martin, Elodie Gouadon, Dominique Desvaux, Franck Bridoux7, Georges Guellae, Pierre Ronco, Philippe Lang, Andre Pawlak and Djillali Sahali (2013). Upregulation of c-mip is closely related to podocyte dysfunction in membranous nephropathy, Kidney International. 46(5), 991-8

Hassan Izzedine, Melanie Mangier, Virginie Ory, Shao-Yu Zhang, Kelhia Sendeyo, Khedidja Bouachi, Vincent Audard, Christine Pe?choux, Jean C. Soria, Christophe Massard, Rastilav Bahleda, Edward Bourry, David Khayat, Alain Baumelou, Philippe Lang, Mario Ollero, Andre Pawlak and Djillali Sahali (2014). Expression patterns of RelA and c-mip are associated with different glomerular diseases following anti-VEGF therapy, Kidney International. 115(18),

Anissa Moktefi, Shao-yu Zhang, Pauline Vachin, Virginie Ory, Carole Henique, Vincent Audard, Catherine Rucker-Martin, Elodie Gouadon, Michael Eccles, Andreas Schedl, Laurence Heidet, Mario Ollero, Djillali Sahali and Andre Pawlak (2016). Repression of CMIP transcription by WT1 is relevant to podocyte health, Kidney International. 584(3), 500-6

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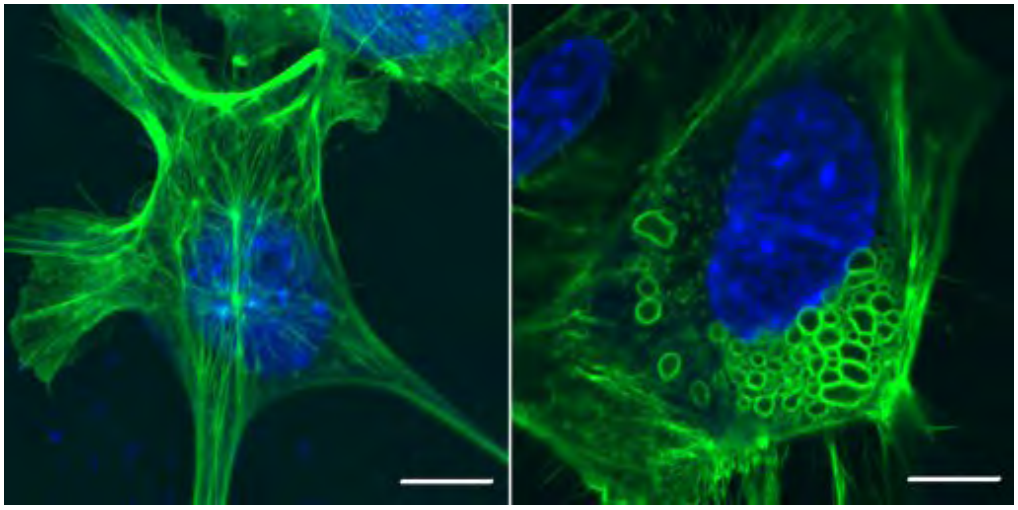
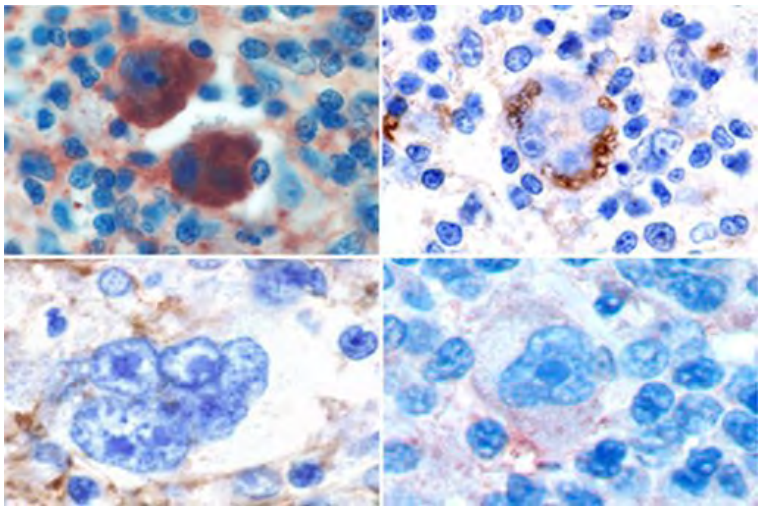
Receptor tyrosine kinase inhibitor (RTKI) sorafenib induces major podocyte cytoskeleton alterations



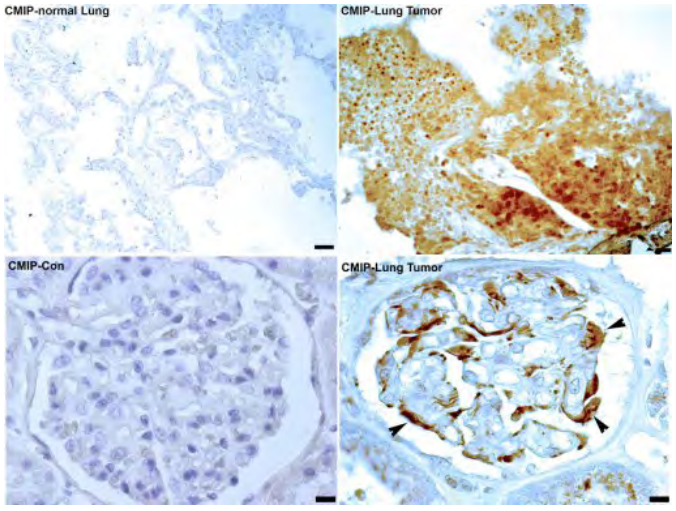
Differentiated podocytes were incubated with either 10 mmol/l sorafenib or the vehicle (control) for 24 h at 37 1C, and then stained for F-actin with fluorescein isothiocyanate-conjugated phalloidin. Scale bar: 20 microm. (Kidney Int. 85: 457-70; 2014)

Overproduction of CMIP in Reed-Sternberg (HRS) cells of patients with idiopathic nephrotic syndrome



(A) Localization of CMIP in HRS cells from patients with idiopathic nephrotic syndrome (INS) revealing Hodgkin lymphoma (HL-INS). (B) no CMIP induction was detected in the HRS cells of patients with isolated HL. Original magnification, X100. (Blood. 115: 3756-3762; 2010).

CMIP induction in patient with idiopathic nephrotic syndrome revealing a small cell Lung Cancer



Localization of CMIP in cancer cells (top level; Scale bar: 50 microm) and in podocytes of a patient with a small cell Lung Cancer (SCLC) (lower level; Scale bar: 20 microm). No CMIP expression was detected in controls. (Am J Kidney Dis. 69: 477-480; 2017).

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Key facts

Team

- Researchers : 3
- Technicians : 0
- Postdoc fellows : 1
- PhD Students : 0

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 0

Keywords

- Chronic Kidney Disease
- Nephrolithiasis
- Hypertension
- Osteoporosis
- Human Studies
- Biomarkers
- Physiological studies
- Immunohistochemistry
- Biochemistry

Dominique Eladari

Pathophysiology of the renal tubule

Université de la Réunion
Inserm UMR1188
Olivier Meilhac
St Denis

> ***Our group propose a unique combination of modern genetic manipulation together with "old but direct" functional techniques to obtain straightforward demonstration of physiological and pathophysiological mechanisms.***

Research Brief :

We are located in Reunion Island, a region of France in which the population is very mixed due to the long history of migration of the Island, and in which during the last decade dramatic changes in the diet has led to a very impressive increase in the prevalence of obesity, diabetes, hypertension and chronic kidney disease. Therefore, our group focuses on the mechanisms leading to the development of diseases in which renal dysfunction is central. We are particularly interested in the effects of the diet on renal homeostasis, on the progression of chronic kidney disease, or on the onset of essential hypertension.

Methodologies Used :

Generation of genetically engineered mice & molecular biology
In vivo metabolic studies
System biology
Biochemistry of proteins
Human studies

Publications

El Moghrabi S, Houillier P, Picard N, Sohet F, Wootla B, Bloch-Faure M, Leviel F, Cheval L, Frische S, Meneton P, Eladari D, Chambrey R (2010). Tissue kallikrein permits early renal adaptation to potassium load., Proceedings of the National Academy of Sciences of the United States of America. 107(30), 13526-31

Leviel F, Hübner CA, Houillier P, Morla L, El Moghrabi S, Brideau G, Hassan H, Hatim H, Parker MD, Kurth I, Kougioumtzes A, Sinning A, Pech V, Riemondy KA, Miller RL, Hummler E, Shull GE, Aronson PS, Doucet A, Wall SM, Chambrey R, Eladari D (2010). The Na+-dependent chloride-bicarbonate exchanger SLC4A8 mediates an electroneutral Na+ reabsorption process in the renal cortical collecting ducts of mice., The Journal of clinical investigation. 120(5), 1627-35

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Gueutin V, Vallet M, Jayat M, Peti-Peterdi J, Cornière N, Leviel F, Sohet F, Wagner CA, Eladari D, Chambrey R (2013). Renal -intercalated cells maintain body fluid and electrolyte balance., The Journal of clinical investigation. 123(10), 4219-31

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Sinning A, Radionov N, Trepiccione F, López-Cayuqueo KI, Jayat M, Baron S, Cornière N, Alexander RT, Hadchouel J, Eladari D, Hübner CA, Chambrey R. (2017). Double Knockout of the Na+-Driven Cl-/HCO3- Exchanger and Na+/Cl- Cotransporter Induces Hypokalemia and Volume Depletion, Journal of the American Society of Nephrology. 28(1), 130-139

Eladari Dominique - dominique.eladari@inserm.fr - +262 6 92 16 38 48

Key facts

Team

• Researchers : 7
• Technicians : 4
• Postdoc fellows : 2
• PhD Students : 3

Translational approaches

• Patents : 0
• Clinical research grants : 3
• Industry partnerships : 3

International research links

• Germany, Greece, UK, Italy, Spain, Poland, Belgium, The Netherlands.

Keywords

• cross-omics
• pediatric renal disease
• chronic kidney disease
• biomarkers
• Renal fibrosis
• animal models
• Translational research
• omics (transcript- proteo-metabol-)
• semi quantitative immunohistochemistry

Biological Resources

• In vivo models
• Biobank (urine, plasma) of individuals with kidney disease.
• Cohort of diabetic type 1 diabetic individuals and cohort of individuals with developmental nephropathies.

Joost Schanstra

Renal fibrosis-mechanisms and detection

Université de Toulouse 3
(Université Paul Sabatier)
Inserm U 1048
Angelo Parini
Toulouse

Development of new concepts of nephroprotection using translational research and state of the art technologies

Research Brief :

Chronic kidney disease (CKD) patient numbers are dramatically rising due to the increased incidence of diabetes and aging reaching today, in 2017, 15% of the general adult population. In contrast to adults in children CKD is mostly due to developmental disease. Individuals, even with early stage CKD, have a significantly increased risk of cardiovascular disease (CVD) complications. Early detection of CKD or prediction of CVD complications and early treatment is key in the clinical management of CKD. We focus our research on the early detection of CKD in both the pediatric and adult population using innovative mostly non-invasive, omics-based, approaches. In parallel we analyze this omics data for the identification of novel targets in CKD using systems medicine and drug repurposing techniques. We believe that such novel approaches will significantly improve the clinical management of individuals, both children and adults, with CKD.

• **Methodologies Used :**

Animals models of CKD (Unilateral ureteral obstruction, Remnant kidney, Glomerulonephritis, Diabetic nephropathy) and AKI (LPS, Hemorrhagic Shock, rhabdomyolysis).
Molecular biology (qPCR, ChipSeq).
Immunohistochemistry (animal and human renal tissue).
Omics: -transcriptomics, proteomics and metabolomics.
Bioinformatics.

Publications

Klein J, Lacroix C, Caubet C, Siwy J, Zürbig P, Dakna M, Muller F, Breuil B, Stalmach A, Mullen W, Mischak H, Bandin F, Monsarrat B, Bascands JL, Decramer S, Schanstra JP. (2013). Fetal urinary peptides to predict postnatal outcome of renal disease in fetuses with posterior urethral valves (PUV)., Sci Transl Med.. 14(5), 198ra106

Faguer S, Chassaing N, Bandin F, Prouheze C, Garnier A, Casemayou A, Huart A, Schanstra JP, Calvas P, Decramer S, Chauveau D. (2014). The HNF1B score is a simple tool to select patients for HNF1B gene analysis., Kidney Int. 86(5), 1007

Schanstra JP, Zürbig P, Alkhalaf A, Argiles A, Bakker SJ, Beige J, Bilo HJ, Chatzikyrkou C, Dakna M, Dawson J, Delles C, Haller H, Haubitz M, Husi H, Jankowski J, Jerums G, Kleefstra N, Kuznetsova T, Maahs DM, Menne J, Mullen W, Ortiz A, Persson F, Rossing P, Ruggenenti P, Rychlik I, Serra AL, Siwy J, Snell-Bergeon J, Spasovski G, Staessen JA, Vlahou A, Mischak H, Vanholder R. (2015). Diagnosis and Prediction of CKD Progression by Assessment of Urinary Peptides., J Am Soc Nephrol.. 26(8), 1999

Klein J, Ramirez-Torres A, Ericsson A, Huang Y, Breuil B, Siwy J, Mischak H, Peng XR, Bascands JL, Schanstra JP. (2016). Urinary peptidomics provides a noninvasive humanized readout of diabetic nephropathy in mice., Kidney Int. 90(5), 1045

Boizard F, Brunchault V, Moulos P, Breuil B, Klein J, Lounis N, Caubet C, Tellier S, Bascands JL, Decramer S, Schanstra JP, Buffin-Meyer B. (2016). A capillary electrophoresis coupled to mass spectrometry pipeline for long term comparable assessment of the urinary metabolome, Sci Rep.. 3(6), 34453

Papadopoulos T, Casemayou A, Neau E, Breuil B, Caubet C, Calise D, Thornhill BA, Bachvarova M, Belliere J, Chevalier RL, Moulos P, Bachvarov D, Buffin-Meyer B, Decramer S, Auriol FC, Bascands JL, Schanstra JP, Klein J. (2017). Systems biology combining human- and animal-data miRNA and mRNA data identifies new targets in ureteropelvic junction obstruction., BMC Syst Biol.. 11(1), 31

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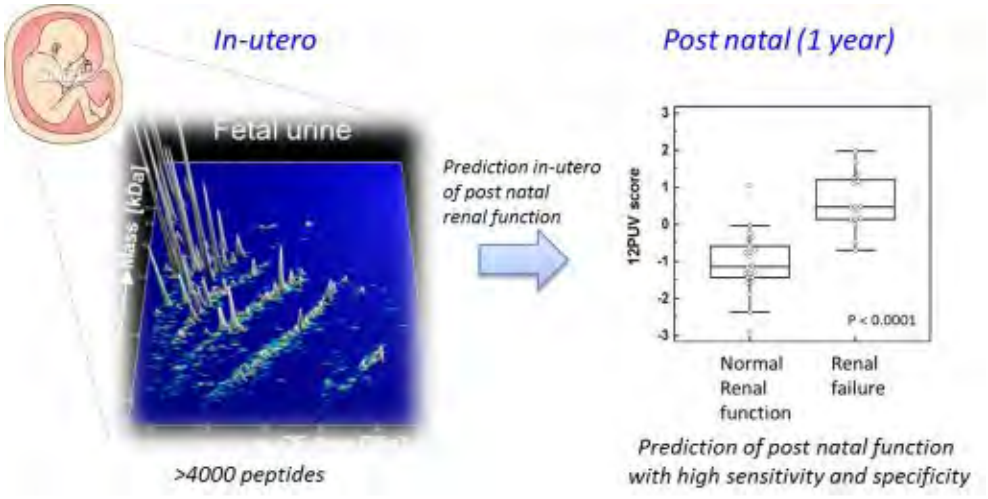
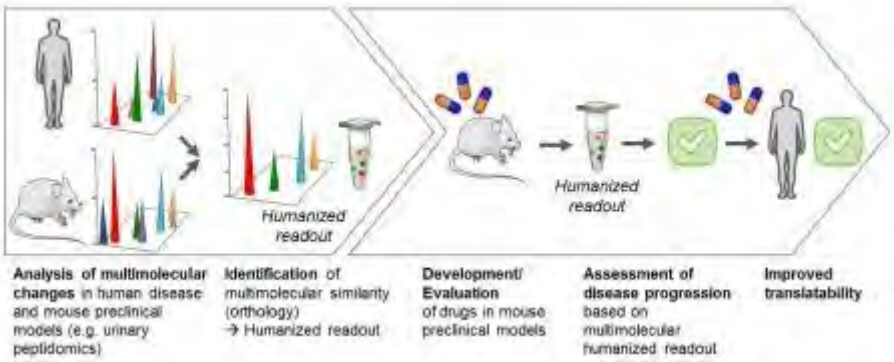
Prenatal prediction of post-natal disease:



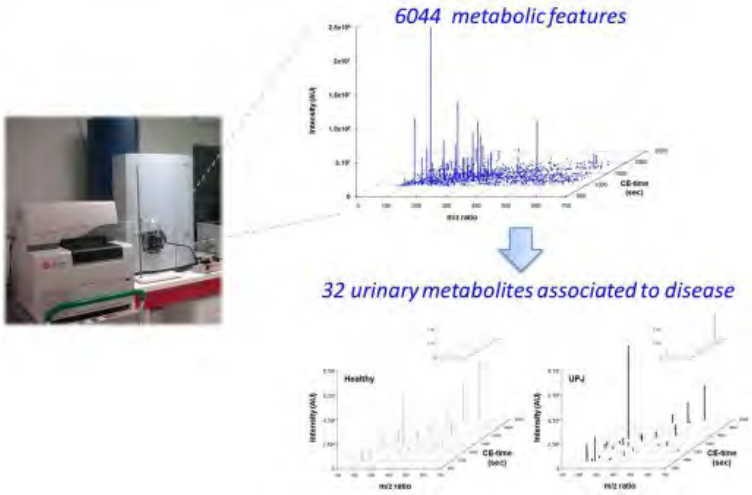
We have been studying the fetal urinary peptidome using capillary electrophoresis coupled to mass spectrometry to identify peptides that predicted in-utero renal function after birth of fetuses with obstructive nephropathy. This led to the identification of a fetal urinary peptide panel composed of 12 peptides (12PUV) allowing prediction of post-natal renal function with high sensitivity and specificity (For details see: Klein et al., Sci Transl Med. 2013).

Speeding up preclinical research:



A major issue in drug research is that many potential drugs work fine in animal models but do significantly less well in humans (or not work at all). To improve on the validity of preclinical observations we have developed a non-invasive multimolecular humanized readout in mice based on molecular signatures similar in mice and humans. Such read-out will allow to find out at an early stage (eg preclinical) whether a new drug is likely to work in humans as well (Klein et al., Kidney International

Reproducible urinary metabolome analysis:



We have been working for many years to setup a robust urinary metabolome analysis pipeline in the laboratory which now has fully maturated. We have shown that we can now analyze the metabolite content of the same sample for over 4 (!) years with high reproducibility mainly based on a unique internal normalization procedure. We have used this pipeline to identify urinary metabolite biomarkers of disease (Boizard et al., Sci Rep. 2016).

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Osteoarticular system

Lyos
Osteoporosis - Bone Metastasis - Lyon

Olivier Peyruchaud

Lysophospholipids and Bone Pathophysiology

Université Claude Bernard
Lyon I
Inserm U1033
Philippe Clézardin
Lyon

Key facts

Team

• Researchers : 3
• Technicians : 2
• Postdoc fellows : 0
• PhD Students : 1

Translational approaches

• Patents : 2
• Clinical research grants : 0
• Industry partnerships : 1

International research links

• USA, Netherlands, Italy, Germany, Hungary, UK, Mexico

Keywords

• Lysophospholipids
• Autotaxin
• Bone
• Inflammation
• Metastasis
• Animal models
• Histology
• Cell biology
• Osteoimmunology
• Imaging

Our team has a unique expertise in developing and analyzing animal models mimicking human bone diseases such as breast cancer bone metastasis (immunodeficient, syngenic, systemic and spontaneous models), osteoporosis (ovariectomy), hypocalcemia (low Ca2+ diet), inflammation (hTNF-Tg mice, LPS, CAIA)

Research Brief :

We have shown in the past that the natural bioactive lipid, lysophosphatidic acid (LPA), derived from platelets or arising from the lysophospholipase activity D autotaxin (ATX) produced by tumor cells, stimulates the growth of breast cancer bone metastasis. Targeting of type 1 receptor of LPA (LPA1) is a therapeutic target for patients with bone metastases. Our recent study of Lpar1-KO mice showed that LPA controls differentiation and osteoclast resorption activity via the LPA1. In addition, we have demonstrated that ATX is a new platelet mediator stimulating metastasis dissemination of tumor cells and that tumor LPA1 exerts a key role in metastasis of breast cells in triple negative cancers through activation of a PI3K/Zeb1/miR-21-dependent pathway. The research project is largely based on comprehensive analyses of global and bone tissue-specific knockout mice to develop a new field of study on the role of lysophospholipids in bone pathophysiology. The project is organized into two themes. In Theme 1 « Role of ATX / LPA in bone physiology » we will study the role of ATX on osteoclastic and osteoblastic functions and cross talks between TGF? and LPA-induced signaling pathways in the control of bone resorption. In the Theme 2 « Role of ATX / LPA in bone pathology » we will exploit relevant animal models for the study of ATX and LPA in osteoporosis, rheumatoid arthritis and bone metastasis.

• **Methodologies Used :**

- Global knock out animals
- Bone cell-specific knock out animals
- Animal experimentation (age-related challenges)
- Microcomputed tomography
- Histology and Immunohistology
- Human and mouse, primary and cell line cultures (osteoclasts, osteoblasts, cancer cells)
- Bioluminescence imaging
- Photonique microscopy
- Confocal microscopy
- qPCR, TLDA
- Protein purification (LPLC)

Publications

Coury F, Annels N, Rivollier A, Olsson S, Santoro A, Speziani C, Azocar O, Flacher M, Djebali S, Tebib J, Brytting M, Egeler RM, Rabourdin-Combe C, Henter JI, Arico M, Delprat C. (2008). Langerhans cell histiocytosis reveals a new IL-17A-dependent pathway of dendritic cell fusion., Nature Medicine. 14(1), 81-7

Coury F, Zenger S, Stewart AK, Stephens S, Neff L, Tsang K, Shull GE, Alper SL, Baron R, Aliprantis AO (2013). SLC4A2-mediated Cl-/HCO3- exchange activity is essential for calpain-dependent regulation of the actin cytoskeleton in osteoclasts., Proc Natl Acad Sci U S A. 110(6), 2163-8

Leblanc R, Lee SC, David M, Bordet JC, Norman DD, Patil R, Miller D, Sahay D, Ribeiro J, Clézardin P, Tigyi GJ, Peyruchaud O. (2014). Interaction of platelet-derived autotaxin with tumor integrin ?V?3 controls metastasis of breast cancer cells to bone., Blood. 124(20), 3141-50

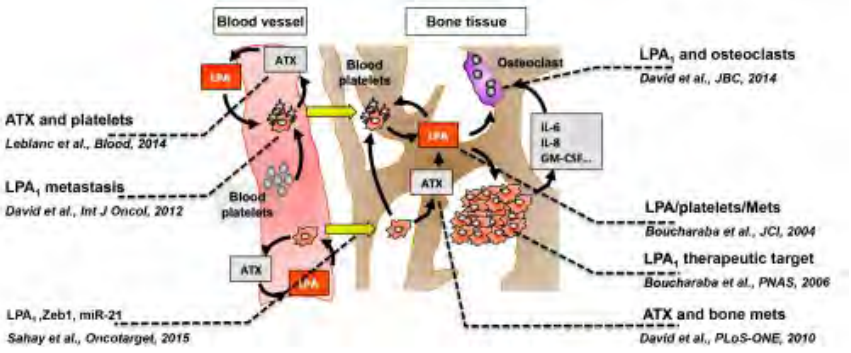
David M, Machuca-Gayet I, Kikuta J,Ottewell P,Mima F, Leblanc R, Bonnelye E, Ribeiro J, Holen I, Lopez Vales R, Jurdic P, Chun J, Clézardin P, Ishii M, Peyruchaud O. (2014). Lysophosphatidic acid receptor type 1 (LPA1) plays a functional role in osteoclast differentiation and bone resorption activity., Journal of Biological Chemistry. 289(10), 6551-64

Sahay D, Leblanc R, Grunewald TG, Ambatipudi S, Ribeiro J, Clézardin P, Peyruchaud O. (2015). The LPA1/ZEB1/miR-21-activation pathway regulates metastasis in basal breast cancer., Oncotarget. 6(24), 20604-20

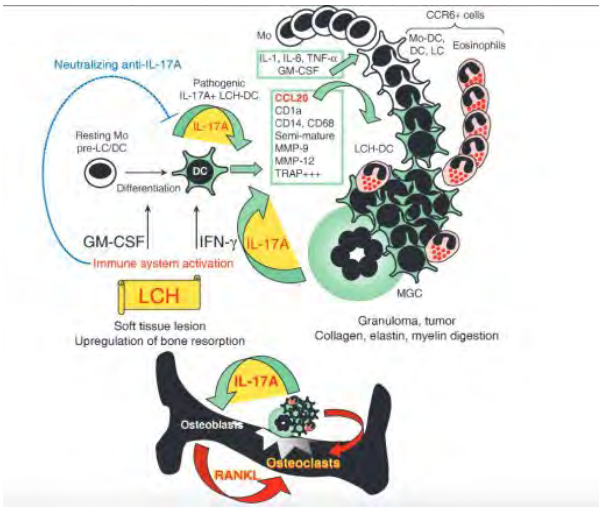
Schwarzer M, Makki K, Storelli G, Machuca-Gayet I, Srutkova D, Hermanova P, Martino ME, Balmand S, Hudcovic T, Heddi A, Rieusset J, Kozakova H, Vidal H, Leulier F. (2016). Lactobacillus plantarum strain maintains growth of infant mice during chronic undernutrition, Science. 351(6275), 854-7

Peyruchaud Olivier - olivier.peyruchaud@inserm.fr - http://www.lyos.fr/

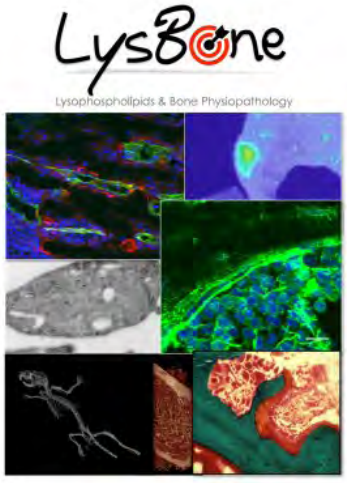
Role of the LPA/ATX track in breast cancer-mediated bone metastasis



Coury et al, Nat Med 2008



Multiple Imaging plateforms available in team LYSBONE (Team 3, INSERM U1033)



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SAINBIOSE
SAnté INgéniérie BIOlogie Saint-Etienne
U1059 • INSERM • SAINT-ETIENNE

Laurence Vico

U1059 - SAINBIOSE

Université de Lyon -
Saint-Etienne (Université Jean Monnet)
Inserm U1059
Laurence Vico
Saint-Etienne

SAINBIOSE studies the chronic pathologies and astronautes for osteo-articular systems through transversal approaches combining fundamental, technological and clinical research.

Key facts

Team

• Researchers : 46
• Technicians : 25
• Postdoc fellows : 10
• PhD Students : 10

Translational approaches

• Patents : 0
• Clinical research grants : 5
• Industry partnerships : 4

International research links

• Italy
• the Netherlands
• Germany

Keywords

• Arthrosis
• Ostéoporosis
• Bone substitutes
• Biomechanics
• Arterial venous disease and coagulation
• Pharmocology of antithrombotics
• microtomography
• spaceflight
• Histomorphometry
• animal models
• cell and tissue imaging
• cellular models

Biological Resources

• Rodent experimental models : immobilisation, exercise, vibrating plates, ovariectomy, marrow-ablation
• In vitro 2D and 3D models of cell culture under mechanical constraint
• sedentary postmenopausal women
under physical training (whole body vibration, golf)
• µCT scans and bone Biomarkers

Research Brief :

Our missions include the understanding of mechanotransduction at the bone and joint level and the use of mechanical stimuli (intrinsic and extrinsic) to control cellular responses to other stresses in the skeletal environment (hormonal, vascular, and energetic).
We analyze mechanical and metabolic deconditioning occurring in extreme (spaceflight and analogs) and disused (osteoporosis, inactivity, osteoarthritis, rheumatoid arthritis, nutrition disorders) conditions. The efficacy and feasibility of pharmaceutical or mechanical treatments is evaluated, including analysis of mechanical transfers and numerical models.
We study the regulation between bone cells and their environment, as the components of the extracellular matrix (SIBLING proteins), growth factors and vascularization of bone. Tools are genetically altered mice, in vivo models (marrow ablation, hyper or hypo-gravity, whole-body vibrations, nutritional disorders, and pharmaceutical treatments) and specific techniques for qualitative and quantitative tissue imaging. In vitro 3D models of osteocytogenesis imitating key aspects of the bone environment are developed, including scaffolds optimized for dedicated bioreactors.

• Methodologies Used :

Microgravity experiments (including space flight)
In vitro and in vivo models of mechanical stimulation (including 2D and 3D cell culture)
In vivo experimental models on rodents
Histology, histomorphometry of undecalcified mineralized tissues
Imaging (photonic microscopy, microtomography)
Bone vascular imaging and bone blood perfusion estimation in mice

Publications

Guignandon A, Faure C, Neutelings T, Rattner A, Mineur P, Linossier MT, Laroche N, Lambert C, Deroanne C, Nusgens B, Demets R, Colige A, Vico L. (2014). Rac1 GTPase silencing counteracts microgravity-induced effects on osteoblastic cells., FASEB J. 28(9), 4077-87

Lavet C, Martin A, Linossier MT, Vanden Bossche A, Laroche N, Thomas M, Gerbaix M, Ammann P, Fraissenon A, Lafage-Proust MH, Courteix D, Vico L. (2016). Fat and Sucrose Intake Induces Obesity-Related Bone Metabolism Disturbances: Kinetic and Reversibility Studies in Growing and Adult Rats., J Bone Miner Res. 31(1), 98-115

Vico L, van Rietbergen B, Vilayphiou N, Linossier MT, Locrelle H, Normand M, Zouch M, Gerbaix M, Bonnet N, Novikov V, Thomas T, Vassilieva G. (2017). Cortical and Trabecular Bone Microstructure Did Not Recover at Weight-Bearing Skeletal Sites and Progressively Deteriorated at Non-Weight-Bearing Sites During the Year Following International Space Station Missions., J Bone Miner Res.. 32(10), 2010-2021

Juignet L, Charbonnier B, Dumas V, Bouleftour W, Thomas M, Laurent C, Vico L, Douard N, Marchat D, Malaval L. (2017). Macrotopographic closure promotes tissue growth and osteogenesis in vitro., Acta Biomater. S1742-7061(17), 30142-3

Gerbaix M, Gnyubkin V, Farlay D, Olivier C, Ammann P, Courbon G, Laroche N, Gential R, Follet H, Peyrin F, Shenkman B, Gauquelin-Koch G, Vico L. (2017). One-month spaceflight compromises the bone microstructure, tissue-level mechanical properties, osteocyte survival and lacunae volume in mature mice skeletons, Sci Rep. 7(1), 2659

Courbon G, Lamarque R, Gerbaix M, Caire R, Linossier MT, Laroche N, Thomas M, Thomas T, Vico L, Marotte H. (2018). Early sclerostin expression explains bone formation inhibition before arthritis onset in the rat adjuvant-induced arthritis model., Sci Rep. 8(1), 3492

Vico Laurence - Laurence.Vico@inserm.fr

Key facts

Team

- Researchers : 18
- Technicians : 7
- Postdoc fellows : 2
- PhD Students : 13

Translational approaches

- Patents : 5
- Clinical research grants : 5
- Industry partnerships : 3

International research links

- Chile
- Germany
- Ireland

Keywords

- Mesenchymal stem cell
- Osteo-articular diseases
- Regeneration
- Aging
- Energetic metabolism
- Embryology and molecular genetic of the zebrafish
- Purification of extracellular vesicles
- isolation and culture of mesenchymal stem cell
- Imaging
- Immunomodulation

Christian Jorgensen

Adult stem cells and regenerative medicine.

Université de Montpellier
Inserm U1183
Christian Jorgensen
Montpellier

> ***We are proposing original biotechnology to restore cartilage tissue with clinical applications***

Research Brief :

The IRMB team is dedicated to explore new pathways in tissue regeneration as well as immunomodulation and pave the way to translational medicine and medicine of the future
Our team aims at the following objectives:
- Understanding the molecular mechanisms involved in regeneration: application to osteo-articular diseases
- Understanding molecular mechanisms for cartilage formation and development of scaffolds for cartilage engineering
- Understanding the immunosuppressive properties of MSC
- Understanding the molecular and cellular basis of epimorphic regeneration
- Studing the effect of MSCs of the microenvironment on the energetic metabolism of target cells through direct mitochondria transfer
- Studing the paracrine effects of aged/senescent MSCs on tissue homeostasis.
- Investigating several aspects of hepatic physiopathology: liver detoxication functions, hepatitis C virus infection, and stem cell differentiation to hepatocytes, using on an original model of primary cultures of human adult hepatocytes (PHH) and other liver cell types, including mesenchymal cells.
- Using stem cells for the treatment of neurodegenerative diseases.

Methodologies Used :

- Cell biology: mesenchymal stem cell and primary chondrocytes, mitochondria transfer, primary human hepatocytes , embryonic stem cells, spheroids, CD4+ T cells, macrophages and B cells, foetal and adult neural stem cells, iPS cell
- Purification of extracellular vesicles
- In vivo murine models: collagenase-induiced osteoarthritis, collagen-induiced arthritis, systemic sclerosis, biodistribution studies, major hepatectomy in mice, Prion disease modelisation
- Mouse embryo culture
- Embryology and molecular genetic of the zebrafish
- Biochemistry: ELISA, immunofluorescence
- Seahorse
- Molecular biology: RT-qPCR, transcriptomic analysis, qPCR on mitochondrial DNA
- Imaging: confocal, bi-photon and time-lapse microscopy, in vivo µCT

Publications

Relaño-Ginès A, Gabelle A, Hamela C, Belondrade M, Casanova D, Mourton-Gilles C, Lehmann S, Crozet C (2013). Prion replication occurs in endogenous adult neural stem cells and alters their neuronal fate: involvement of endogenous neural stem cells in prion diseases., PLoS Pathog. 2013(9(8)), e1003485

Caicedo A, Fritz V, Brondello JM, Ayala M, Dennemont I, Abdellaoui N, de Fraipont F, Moisan A, Prouteau CA, Boukhaddaoui H, Jorgensen C, Vignais ML. (2015). MitoCeption as a new tool to assess the effects of mesenchymal stem/stromal cell mitochondria on cancer cell metabolism and function., Sci Rep. Mar 13(5), 9073

Nguyen-Chi M, Laplace-Builhe B, Travnickova J, Luz-Crawford P, Tejedor G, Phan QT, Duroux-Richard I, Levraud JP, Kissa K, Lutfalla G, Jorgensen C, Djouad F. (2015). Identification of polarized macrophage subsets in zebrafish., Elife. Elife(4), e07288

Maumus M, Roussignol G, Toupet K, Penarier G, Bentz I, Teixeira S, Oustric D, Jung M, Lepage O, Steinberg R, Jorgensen C, Noel D. (2016). Utility of a Mouse Model of Osteoarthritis to Demonstrate Cartilage Protection by IFN?-Primed Equine Mesenchymal Stem Cells., Front Immunol. Sep 27(7), 392

Cosenza S, Toupet K, Maumus M, Luz-Crawford P, Blanc-Brude O, Jorgensen C, Noël D. (2018). Mesenchymal stem cells-derived exosomes are more immunosuppressive than microparticles in inflammatory arthritis., Theranostics. Feb 3(8(5)), 1399-1410

Despeyroux A, Duret C, Gondeau C, Perez-Gracia E, Chuttoo L, de Boussac H, Briolotti P, Bony C, Noël D, Jorgensen C, Larrey D, Daujat-Chavanieu M, Herrero A. (2018). Mesenchymal stem cells seeded on a human amniotic membrane improve liver regeneration and mouse survival after extended hepatectomy., J Tissue Eng Regen Med.. Apr(12(4)), 1062-1073

Jorgensen Christian - christian.jorgensen@inserm.fr

Key facts

Team

• Researchers : 6
• Technicians : 8
• Postdoc fellows : 0
• PhD Students : 3

Translational approaches

• Patents : 3
• Clinical research grants : 2
• Industry partnerships : 4

International research links

• Germany
• UK
• Chile

Keywords

• Regulatory T cells
• Arthritis
• (Auto)inflammation
• Genetic
• Monocytes
• Animal models of arthritis
• Multiparametric flow cytometry
• Molecular biology
• Cell biology
• functional genomic

Florence Apparailly

Genetic and immunopathology of inflammatory osteoarticular diseases

Université Montpellier
Inserm U1183
Christian Jorgensen
Montpellier

The combination of clinicians, geneticists and biologists around the theme of (auto)inflammatory disorders.

Research Brief :

Gathering skills for genetic, functional genomic, molecular and cellular immunology, gene and cell therapy, our team aims at the following objectives:
1- Identify genes associated with chronic inflammatory disorders with rheumatic tropism and study their role in pathophysiological conditions
2- Better characterize distinct sub-populations of monocytes and regulatory T cells and identify pathways controlling their differentiation and function in chronic inflammatory and osteoarticular disorders
3- Propose innovative strategies to restore immune tolerance using tolerogenic myeloid cells or induced Treg cells.

• **Methodologies Used :**

Next generation sequencing - Exome sequencing - miRNome - Transcriptomics - Functional genomics - Multi-parametric flow cytometry - Cell sorting - Human and mouse immuno-monitoring - Experimental models of inflammation (monitoring of clinical, immunological, histopathological and bone architecture parameters) - Isolation and in vitro functional characterization of regulatory T cells, dendritic cells, M1/M2 macrophages and osteoclasts - In vitro and in vivo RNAi - Gain and loss of function studies - Reporter systems for validation of miRNA targets - SeaHorse

Publications

Présumey J, Courties G, Louis-Plence P, Escriou V, Scherman D, Pers YM, Yssel H, Pène J, Kyburz D, Gay S, Jorgensen C, Apparailly F. (2013). Nicotinamide phosphoribosyltransferase/visfatin expression by inflammatory monocytes mediates arthritis pathogenesis., Ann Rheum Dis. (),

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U1173
INFECTION ET
INFLAMMATION

Maxime Breban

IRIS: Inflammatory Reaction and Immune System / Chronic inflammation and immune system

Université de Versailles
Saint-Quentin en Yvelines Université Paris Saclay
Inserm UMR 1173
Jean-Louis Herrmann
Saint-Quentin en Yvelines

Our research offers a unique opportunity in arthritic diseases to link inflammation and immune system based on a multidisciplinary approach which involves a two-way process going back and forth between genetic data, immunological mechanisms and the transfer of the findings to the clinic

Key facts

Team

- Researchers : 8
- Technicians : 4
- Postdoc fellows : 2
- PhD Students : 4

Translational approaches

- Patents : 0
- Clinical research grants : 2
- Industry partnerships : 2

International research links

- Belgique
- Allemagne
- Australie

Keywords

- autoimmunity
- Chronic inflammatory diseases
- dendritic cell
- genetical genomics
- genetics
- transcriptomics
- cell biology
- imaging

Research Brief :

Three main pillars constitute the organisation of our research program:
- Genomic analysis with diagnostic and therapeutic applications,
- Functional validation of targets,
- Animal models.

Chronic inflammatory diseases result from perturbations of effector cells and soluble mediators of the immune system, and local target tissue abnormalities. The precise mechanisms leading to inflammation in these diseases are incompletely understood and treatments inadequate. The aim of our team is to increase understanding of mechanisms of chronic inflammation. Our goals are: the identification of new genes of susceptibility, and their functional characterization.
These diseases show a strong involvement of the major histocompatibility complex. Because much remains to be learnt on the role of this region in autoimmunity, we are developing specific researches on this topic by focusing on spondylarthritis, autoimmune myasthenia gravis that show a strong association with the MHC and soon on rheumatoid arthritis.
Starting from clinical investigations, and based on genetic and genomic approaches, we use in vitro cellular assays or suitable animal models, as needed. The functional role of dendritic cells and myeloid suppressor cells are analysed. Several targets are already studied. The interactions between scientists and physicians in the team and our large collaborative network contribute importantly to the translation of fundamental research into clinical application.

- **Methodologies Used :**

Transcriptomics
Genetics
Molecular biology
Cell Biology
Biochemistry

Publications

Araujo LM, Fert I, Jouhault Q, Labroquère K, Andrieu M, Chiocchia G, Breban M. (2014). Increased production of interleukin-17 over interleukin-10 by treg cells implicates inducible costimulator molecule in experimental spondyloarthritis., Arthritis Rheumatol.. 66(9), 2412-2422

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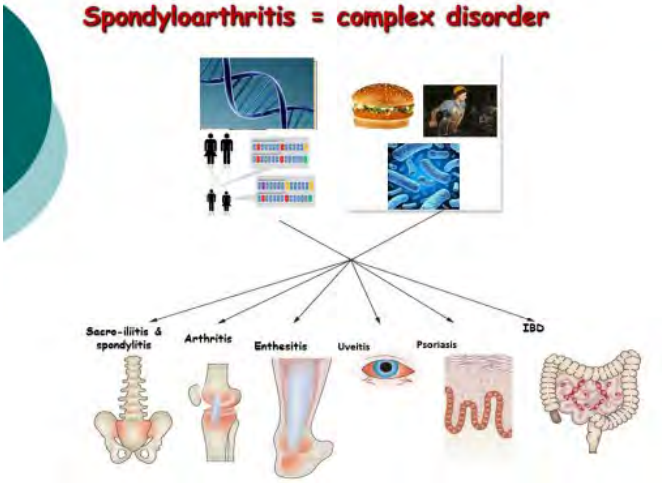
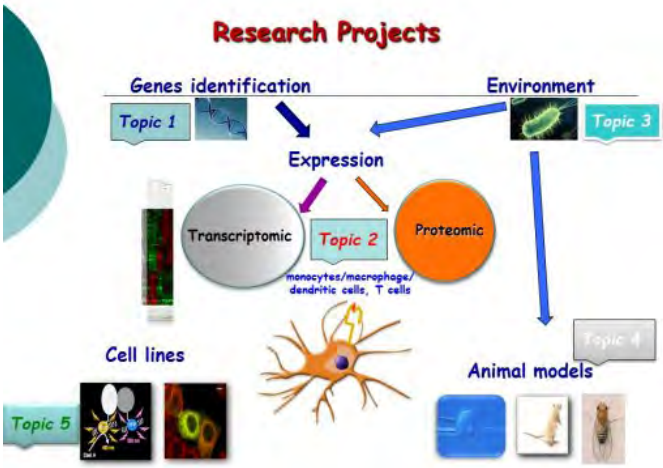
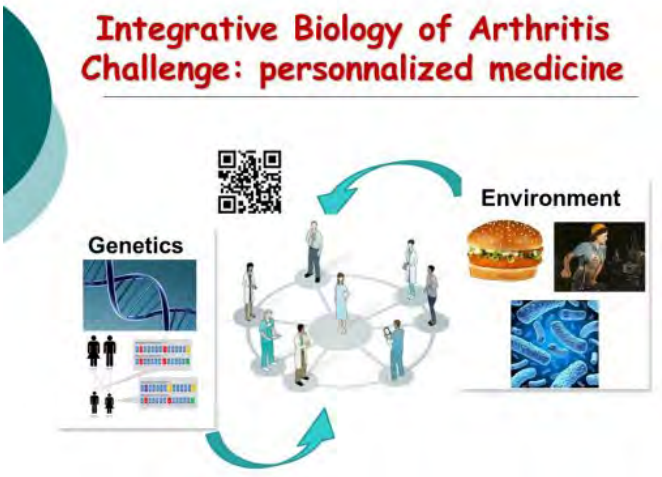
Spondyloarthritis = complex disorder



Research projects



Integrative Biology of Arthritis



Breban Maxime - maxime.breban@aphp.fr - 0149095672/74

Key facts

Team

- Researchers : 1
- Technicians : 1
- Postdoc fellows : 1
- PhD Students : 2

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 1

International research links

- United States

Keywords

- Bone
- Muscle
- Skeletal Regeneration
- Stem Cell
- Bone Morphogenetic Proteins
- Mouse genetics
- Histology/histomorphometry
- Immunohistochemistry
- Flow cytometry
- Transcriptome

Biological Resources

- Mouse models of bone repair
- Mouse transgenic/KO models
- Primary stem cell cultures

Céline Colnot

Origins and functions of skeletal stem cells in bone regeneration

Université de Paris 05
(Université Rene Descartes)
Inserm UMR1163
Stanislas Lyonnet
Paris

We combine expertise in mouse models of bone regeneration, genetically modified mice, primary stem cell culture, cellular and molecular analyses to characterize the role of skeletal stem cells in tissue regeneration and repair.

Research Brief :

The goal of our research is to understand the basic cellular and molecular mechanisms of skeletal regeneration. We aim to define the origins of skeletal stem cells, the factors regulating their recruitment at the bone injury site, and the ontogeny of skeletal stem cells. We showed that the local periosteum (the tissue lining the outer surface of bone) is a key source of skeletal progenitors and that periosteum-muscle interactions are critical for bone repair.
Two main projects:
-Role of periosteum and mesenchymal lineages in skeletal regeneration: (1) characterize the skeletal stem cell populations within adult bone marrow and periosteum, and their embryonic origins, (2) compare the regenerative capacities of skeletal stem cells, (3) assess the molecular regulation of skeletal cell fate decisions during bone repair.
- Role of bone-muscle interactions in musculoskeletal repair: (1) identify the cellular contributions of skeletal and muscle lineages to musculoskeletal repair, (2) determine the role of Bone Morphogenetic Proteins in mediating bone-muscle interactions and (3) identify new factors mediating bone-muscle cross talks.
Our research has implications for cell-based and drug-based therapies in skeletal regeneration and the treatment of various diseases of the skeleton.

Methodologies Used :

- Mouse models of bone regeneration (tibial fracture, cortical defects, segmental defects, bone/muscle grafting, musculoskeletal injuries)
- Renal capsule transplantation
- Genetically modified mice
- Histology, histomorphometry, immunohistochemistry
- Primary skeletal stem cell culture
- Flow cytometry
- Transcriptome analyses

Publications

Colnot C (2009). Skeletal cell fate decisions within periosteum and bone marrow during bone regeneration., Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research. 24(2), 274-82

Yu YY, Lieu S, Lu C, Colnot C (2010). Bone morphogenetic protein 2 stimulates endochondral ossification by regulating periosteal cell fate during bone repair., Bone. 47(1), 65-73

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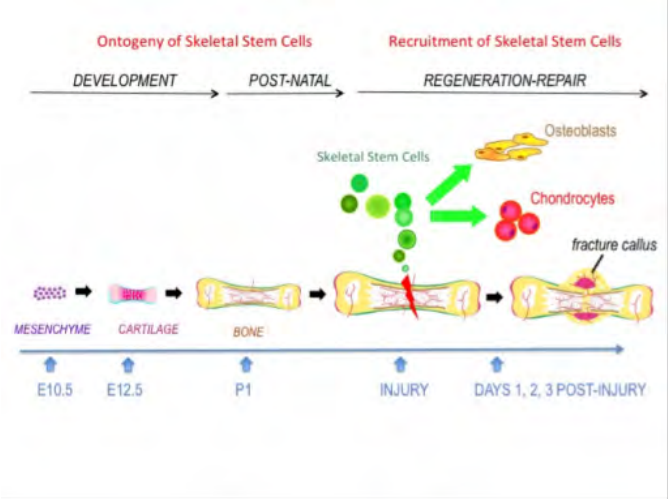
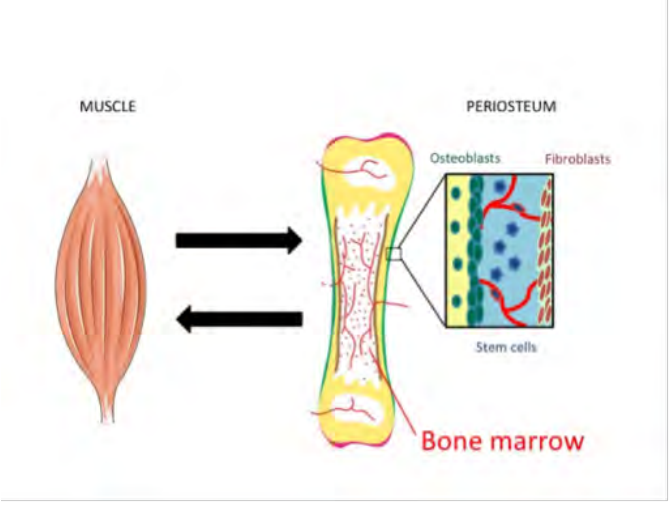
Origins of skeletal stem cells and recruitment after bone injury



Muscle-bone interactions in musculoskeletal regeneration



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http://www.institutimagine.org/en/research/25-research-labs/114-origins-and-functions-of-skeletal-stem-cells-in-bone-regeneration.html

Key facts

Team

• Researchers : 12
• Technicians : 7
• Postdoc fellows : 4
• PhD Students : 5

Translational approaches

• Patents : 1
• Clinical research grants : 3
• Industry partnerships : 2

International research links

• USA Birmingham, Alabama - Leeds, UK - Brazilia, Brazil - Carabobo, Venezuela - Ho Chi Min, Vietnam

Keywords

• oral medicine
• Genetics
• Environment
• Mineralization
• Physiopathology
• Tissue reconstruction

Biological Resources

• Cultures of oral mineralized tissue forming cells.
• Collection of Human Odontogenic Tissues.
• Cohort of Rare Facial and Buccal Malformation Center (national network and ERN)
• Transgenic mouse models of oral malformations.

Ariane Berdal Sylvie Babajko

Molecular Oral Physiopathology

Université de Paris 07
(Université Denis Diderot) Université de Paris 05
(Université Paris Descartes)
CHU Inserm U 1138
Pascal Ferré
Paris

Tranlational researches are conducted from involved genes to in vitro cell biology, animal models and clinics.

Research Brief :

Our group is dedicated to the oral-facial area, an exemplary composite skeleton where epithelial and neurectoderm-derived mesenchymal cells cooperate within a permanently challenged microenvironment. Post-natal physiology harbours specificity (dental cells, bone drug sensitivity and fate related to odontogenic growth and tumours) which determinants are studied in our group. Homeogene patterns were shown to imprint oral cells and impact their post-natal proliferation, differentiation and functions. This was illustrated in transgenic mice: the combinatorial Msx2, Dlx1, 3, 4, 6 interplay defined the frame of matrix protein expression and thus, regional enamel thickness. Msx1 and Msx2 controlled site-specifically osteoblast/osteoclast cross-talks and activity during physiology and healing. Msx/Dlx transcriptional role is explored on dental and bone genes. An endogenous antisense cis-RNA for Msx1 was discovered by us. Epigenetic and cell-autonomous mechanisms were evidenced and are presently analysed from sense and antisense promoters to an integrated level. Based on this detailed cell profiles, innovative biomaterials are tested as well some hormonal and toxic factors controlling skeletal morphogenesis. Correspondingly, human rare diseases are studied in our Reference Center. The team is involved in training programs which welcome scientists and health students in oral and mineralised tissue research.

• **Methodologies Used :**

Molecular in situ studies on mineralized tissues and cells.
2D and 3D analysis of the dento-maxillo-facial skeleton.
Oral and dental genetics - rare diseases
Experimental surgery and material investigation.
Molecular and cellular Biology.

Publications

Jedeon K., De la Dure-Molla M., Brookes S.J., Loiodice S., Marciano C., Kirkham J., Canivenc-Lavier M.C., Boudalia S., Bergès R., Harada H., Berdal A., Babajko S. (2013). Enamel defects reflect perinatal exposure to bisphenol A, Am. J. Pathol.,. 183(1), 108-18

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Berdal Ariane - ariane.berdal@crc.jussieu.fr - 00 33 1 44 27 55 90 (82)

Key facts

Team

- Researchers : 4
- Technicians : 2
- Postdoc fellows : 0
- PhD Students : 1

Translational approaches

- Patents : 1
- Clinical research grants : 5
- Industry partnerships : 3

International research links

- Australia
- United States
- Belgium

Keywords

- Cartilage
- Osteoarthritis
- Intervertebral disc
- Arthritis
- Mechanical stress
- Pathological calcifications
- Cell culture
- Animal models
- Molecular biology
- Cell biology

Biological Resources

- Human, rabbit and mouse primary cell cultures (articular chondrocytes, growth plate chondrocytes, intervertebral disc cells)
- Arthritis mouse model
- Human normal and osteoarthritic cartilage

Prof François Rannou

Pharmacology, Toxicology, Cell Signaling of Cartilage and Intervertebral Disc

Sorbonne Paris Cité,
Université Paris Descartes,
Faculté des Sciences
Fondamentales et Biomédicales
INSERM UMR-S 1124
Prof Robert Barouki
Paris

Our group combines the skills of biologists, biochemists, biophysicists and clinicians devoted to the biological understanding of cartilage diseases. Associated to extensive and strong collaborations, this situation allows us to design targeted non-pharmacological and pharmacological treatments.

Research Brief :

Our group has developed a general expertise in pharmacology, toxicology, cell signaling of cartilage and intervertebral disc and an original expertise in the field of joint diseases such as arthritis, osteoarthritis and scoliosis using specific in vitro models (chondrocytes, synoviocytes) and animal models. Indeed, in order to deliver specific treatment for intervertebral disc and cartilage diseases, the first step is to better understand the pathogenesis of intervertebral disc and cartilage disorders. The originality ofour group is to be directly connected with clinicians from Assistance Publique-Hôpitaux de Paris Hospitals as the group leader (Prof François Rannou) is the head of the department of Physical Medicine and Rehabilitation of Cochin Hospital, Paris, France. This specificity allows access to human tissues from finely phenotyped patients. Prof Francois Rannou has an expertise in in vitro experiments, mechanotransduction and clinical evaluation of patients, Prof Didier Borderie in in vitro experiments regarding human synoviocytes, Assoc Prof Christelle Nguyen in developmental biology and clinical evaluation of patients, and Dr Francois Étienne (Research Engineer) in animals breeding, primary cell cultures and mechanotranduction.

- **Methodologies Used :**

Our approach is multidisciplinary, involving in vivo/in vitro models related to osteoarthritis, arthritis and intervertebral disc diseases, disease-modeling transgenic mice, molecular biology, biochemistry, pharmacology and cell biology and histology (classic microscopy and time-lapse live microscopy, immunocytofluorescence and optical/laser microscopy coupled to deconvolution analysis).
In vitro experiments are performed using mesenchymal stem cell lines and primary cultures of rabbit, mouse, and human articular chondrocytes and intervertebral disc cells. Our primary culture conditions are selective for physiological tissue conditions (normoxia vs hypoxia; hormonal conditions; static vs dynamic mechanical stress conditions).

Publications

Ottaviani S, Tahiri K, Frazier A, Hassaine ZN, Dumontier MF, Baschong W, Rannou F, Corvol MT, Savouret JF, Richette P (2010). Hes1, a new target for interleukin 1beta in chondrocytes, Ann Rheum Dis. 69(8), 1488-94

Ombetta JE, Thelier N, Dong CZ, Plocki S, Tsagris L, Rannou F, Massicot F, Djimdé A, El-Hayek E, Shi Y, Heymans F, Gresh N, Chauvet C (2010). Design of group IIA secreted/synovial phospholipase A(2) inhibitors: an oxadiazolone derivative suppresses chondrocyte prostaglandin E(2) secretion, PLoS One. 5(6), e10914

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Nguyen C, Boutron I, Baron G, Sanchez K, Palazzo C, Benchimol R, Paris G, James-Belin É, Lefèvre-Colau MM, Beaudreuil J, Laredo JD, Béra-Louville A, Cotten A, Drapé JL, Feydy A, Ravaud P, Rannou F, Poiraudeau S (2017). Intradiscal Glucocorticoid Injection for Patients With Chronic Low Back Pain Associated With Active Discopathy: A Randomized Trial, Ann Intern Med. 166(8), 547-556

Rannou Prof François - francois.rannou@aphp.fr - +33158412535 - http://umrs1124.biomedicale.parisdescartes.fr/nos-equipes-de-recherche/equipe-2/

Martine Cohen-Solal

Bone - Cartilage and environment

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Inserm U1132
Martine Cohen-Solal
Paris

Key facts

Team

- Researchers : 13
- Technicians : 7
- Postdoc fellows : 5
- PhD Students : 10

Translational approaches

- Patents : 1
- Clinical research grants : 3
- Industry partnerships : 4

International research links

- Europe
- Vietnam

Keywords

- osteoarthritis
- osteoporosis
- cartilage
- Bone
- biobank and patients
- molecular signature
- histology
- bone imaging
- clinical trials

Biological Resources

- Transgenic mice for bone
- Biobank
- Cartilage and bone collection

Physiopathology and Identification of target molecules that regulate bone and cartilage remodeling: from mice to patients

Research Brief :

The research unit has been dedicated to the pathophysiology of bone and cartilage diseases and the expertise have positioned the unit as a leader in the field. Our aim is to characterize the mechanisms that regulate bone and cartilage matrix and to identify the molecular targets that result in the development of osteoporosis and osteoarthritis. The different approaches conducted by the scientists and the clinicians actively involved prompted to the development of tools used from basic to translational research. We have therefore validated biochemical and molecular techniques, cellular and animal models that are then translated in humans through a collection of bone and cartilage tissues as well as mouse and human serum and synovial samples.
To identify molecules involved in joint diseases, different projects are under investigation:
- Role of the proteoglycan in cell-cell interactions with bone and cartilage microenvironment.
- Mechanisms of interaction between bone and cartilage to characterize the role of bone cells such as osteoclasts in mechanical-induced osteoarthritis. We focus on the role of Wnt molecules involved in the bone-cartilage crosstalk.
- Characterization of microcrystalline stress on the cartilage and the role of microcrystals in chondrocyte metabolism and apoptosis. This work is translated to humans samples and to a cohort.
- The regulation of chondrocyte function by autocrine and paracrine factors.

• **Methodologies Used :**

- Primary culture of mouse and human bone cells (osteoclasts, osteoblasts, osteocytes), bone resorption and formation assays, pit assays, bone explants.
- Cultures of primary mouse and human chondrocytes and cartilage explants.
- Cell phenotyping (qRT-PCR, Western-blot, proteolytic activity, ELISA, ARN interference, immunocytology, apoptosis assay, cell imaging)
- Histology analysis (histology, immunohistochemistry, analysis of non decalcified bone)
- Characterisation of systemic bone and subchondral bone (microarchitecture, µCT, bone density)
- In vivo model for murine osteoporosis and osteoarthritis.

Publications

Bouaziz W, Sigaux J, Modrowski D, Devignes CS, Funck-Brentano T, Richette P, Ea HK, Provot S, Cohen-Solal M, Haÿ E (2016). Interaction of HIF1? and ?-catenin inhibits matrix metalloproteinase 13 expression and prevents cartilage damage in mice., Proc Natl Acad Sci U S A. 10(113), 5453-8

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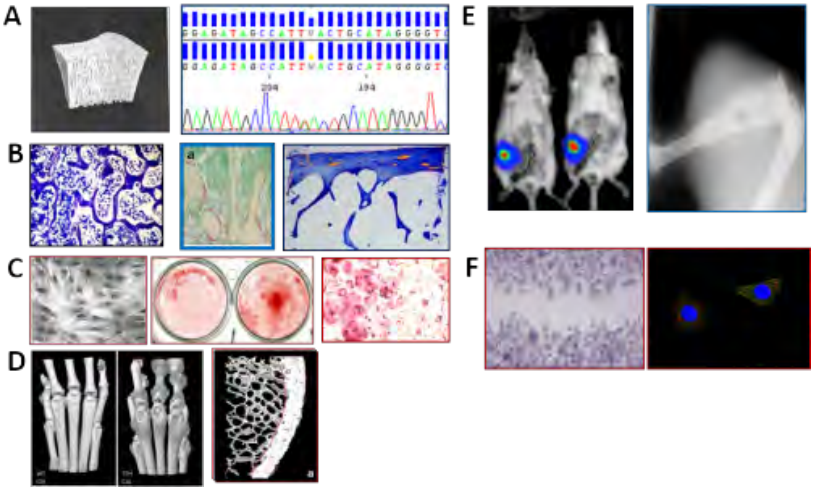
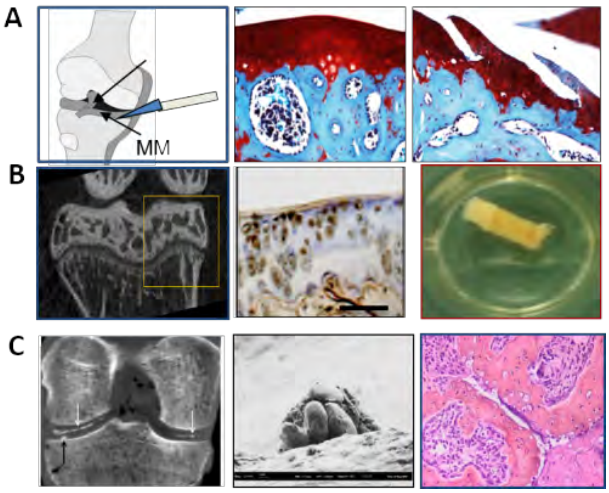
Illustrations of studies on bone



A: Characterisation of microarchitectural changes of bone in young patients with idiopathic osteoporosis. Structural analysis of cortical and trabecular bone is performed by high resolution peripheral quantitative computated tomography and correlated to the genotype (NGS panel)
B: Histomorphometric analysis of cortical and trabecular bone of human and murine undecalcified bone samples
C: Cultures of bone cells (osteoblasts and osteoclasts) and functional tests of bone formation and resorption
D: Evaluation of bone resorption related to inflammation in murine arthritis model (microcomputated tomography).
E: Quantification of bone metastasis by bioluminescence technique and syngenic model of osteosarcoma.
F: Migration test and protein localisation

Illustrations of some studies on cartilage pathology



A: Murin model of joint instability (DMM) that induces a progressive loss of cartilage and osteoarthritis.
B: Analysis of subchondral bone by computed tomography; immunohistochemistry of cartilage; culture of bone and cartilage explants.
C: Microcrystal related joint diseases: characterization of calcifications of meniscus, joint crystals and histology of joints

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CENTRE DE RECHERCHE SAINT-ANTOINE | PARIS

Francis Berenbaum

Metabolic diseases and age-related joint diseases

Université de Paris 06
(Université Pierre et Marie Curie)
Inserm U 938
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Paris

Our team associates physiologists, cell biologists and clinicians devoted to find new targets and new biomarkers in osteoarthritis, particularly by exploring the role of metabolic diseases, mechanical stress and bone/cartilage/synovial tissue interactions

Key facts

Team

• Researchers : 4
• Technicians : 2
• Postdoc fellows : 2
• PhD Students : 2

Translational approaches

• Patents : 1
• Clinical research grants : 2
• Industry partnerships : 2

International research links

• The Netherlands (Leiden University and Amsterdam University)

Keywords

• biomarkers
• cell differentiation
• bone
• synovial tissue
• cartilage
• osteoarthritis
• adipose tissue
• inflammation
• cellular biology
• molecular biology
• histology
• human cohort of hand osteoarthritis
• murine models of osteoarthritis

Biological Resources

• osteoarthritis mouse model
• BioJoint (a biobank of human joint tissues)
• DIGICOD (a cohort of patients with hand OA)
• Human, mouse, rabbit and rat primary culture (articular chondrocyte, costal chondrocyte, osteoblasts)

Research Brief :

Our team has been interested for several years in the physiopathology of osteoarthritis in the final objective to discover innovative treatments and novel diagnostic and prognostic biomarkers. For these objectives, we have developed several tools, from cell cultures to human cohort (DIGICOD, a cohort of hand osteoarthritis patients), from preclinical murine models to joint tissue analysis (BioJoint, a biobank of human joint tissues). We focus our projects on the relationship between osteoarthritis and metabolic diseases. Four main projects are currently under investigation:
1 - Role of bone-secreted 14-3-3epsilon protein on cartilage degradation
2 - Role of chondrocyte differentiation on the angiogenesis of the subchondral bone
3 - Role of the parasympathetic system in joint protection
4 - Role of adipose tissues in OA pathophysiology

• **Methodologies Used :**

- Experimental in vivo model of osteoarthritis
- Histological analysis of joint tissues
- Application of mechanical stress on cartilage explants and bone (Flexercell apparatus)
- Cellular analysis (Western-blot, proteolytic activity, ELISA, qRT-PCR, ARN interference, immunocytology)
- Primary culture of articular chondrocytes (mouse, human) and costal chondrocytes (mouse), of murine osteoblasts (membrane 3D) and of human synoviocytes
- Control of chondrocyte phenotype (hypertrophic differentiation and fibroblastic dedifferentiation)

Publications

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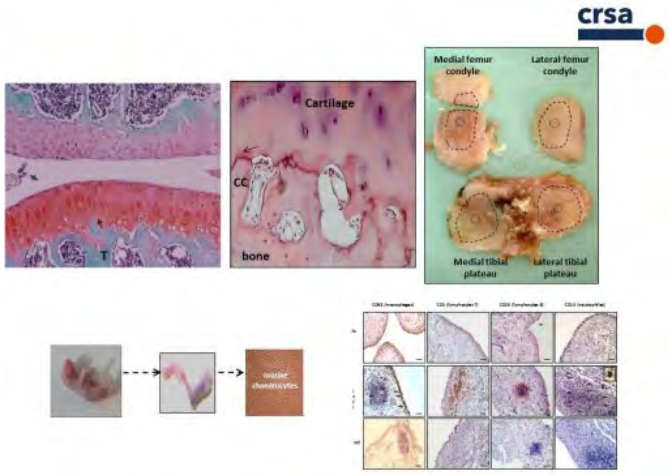
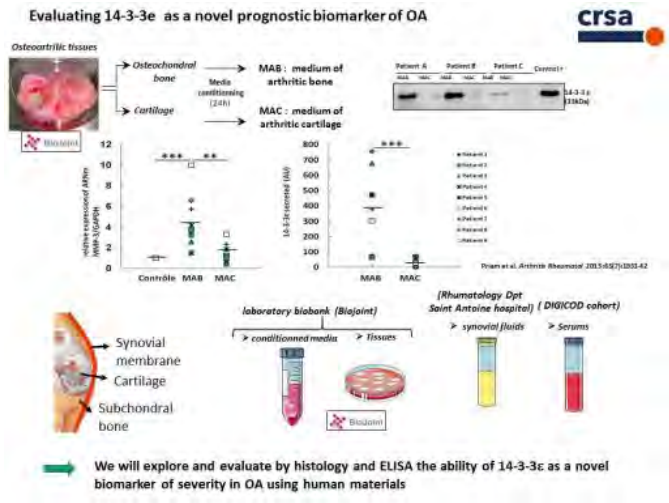
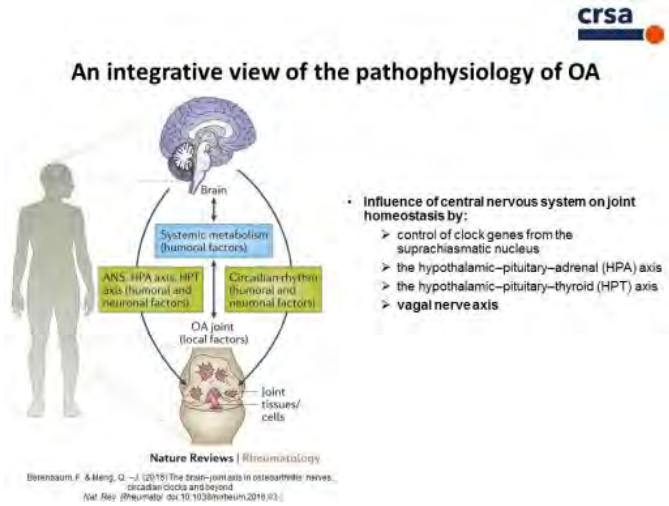
Images obtained in the lab



Tools for research



Basis for an integrative view of the pathophysiology of osteoarthritis



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institut Valrose Biologie

Jean-Claude Scimeca

BIPOA, BioIngénierie et Physiopathologie Ostéo-Articulaire

UCA, Université Côte d'Azur
Inserm U1091 CNRS UMR7277
Stéphane Noselli
Nice

Key facts

Team

- Researchers : 4
- Technicians : 2
- Postdoc fellows : 0
- PhD Students : 2

Translational approaches

- Patents : 0
- Clinical research grants : 0
- Industry partnerships : 0

Keywords

- Bone Physiopathology
- Bone Reconstruction
- Bone Cancer
- Bone Tissue Models
- Bone Defect Models

Gathering researchers, clinicians and industrial partners, we aim at developing and transferring into clinic innovative therapeutic solutions for the treatment of musculoskeletal conditions.

Research Brief :

Our project is focused on bone tissue physiopathology and reconstruction in traumatic, tumoral, and aging situations. Within this context, we aim at developing and transferring into clinic innovative therapeutic solutions for the treatment of musculoskeletal conditions.
The main objectives of our experimental work are: (i) to develop calcium phosphate-based new bone substitutes for bone reinforcement and reconstruction; (ii) to design biomaterials incorporating therapeutic compounds targeting bone tumours; (iii) to decipher the molecular mechanisms underlying new bone formation in traumatic and tumoral environments; (iv) to engineer innovative in vitro 3D models of bone-like constructs, as well as in vivo bone cancer models, based on the use of bone substitutes we develop; (v) to use our models to address basic questions about bone cells and cancer cells interactions with each other and with their microenvironment.
In the future, we will continue to use bone substitutes as drug delivery systems to improve bone strengthening and bone reconstruction. We will also investigate strategies involving the combination of these therapeutic agents to enhance their action. Lastly, to identify new therapeutic targets, these bioactive biomaterials will be used to set up in vitro 3D scaffolds allowing us to document the underlying molecular mechanisms governing bone cells and cancer cells interactions within a bone-like microenvironment.

• Methodologies Used :

With a view towards building normal or metastatic bone tissue niches, we designed several 2D-3D cell culture models combining calcium phosphate-based biomaterials and either bone or cancer cells. Moreover, we take advantage of both in vitro and in vivo models for the screening of therapeutic compounds that could improve the treatment of bone defects after traumatic or cancer lesions. We are also interested in triggering the host immune response against tumour cells. In this attempt, in vivo cancer models are used to identify therapeutic targets among chemokines and chemokine receptors, which are key partners regulating the interactions among bone, immune system, and cancer cells.

Publications

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E. Guillemot, B. Karimdjee-Soilihi, E. Pradelli, M. Benchetrit, E. Goguet-Surmenian, M.A. Millet, F. Larbret, J.F. Michiels, D. Birnbaum, P. Alemanno, H. Schmid-Antomarchi, A. Schmid-Alliana (2012). CXCR7 receptors facilitate the progression of colon carcinoma within lung not within liver, Br J Cancer. 107(12), 1944-9

E. Goguet-Surmenian, P. Richard-Fiardo, E. Guillemot, M. Benchetrit, A. Gomez-Brouchet, P. Buzzo, B. Karimdjee-Soilihi, P. Alemanno, J.F. Michiels, A. Schmid-Alliana, H. Schmid-Antomarchi (2013). CXCR7-mediated progression of osteosarcoma in the lungs, Br J Cancer. 109(6), 1579-85

E. Verron, H. Schmid-Antomarchi, H. Pascal-Mousselard, A. Schmid-Alliana, J.C. Scimeca, J.M. Bouler (2014). Therapeutic strategies for treating osteolytic bone metastases, Drug Discov Today. 19(9), 1419-26

I. Strazic-Geljic, I. Guberovic, B. Didak, H. Schmid-Antomarchi, A. Schmid-Alliana, F. Boukhechba, J.M. Bouler, J.C. Scimeca, E. Verron (2016). Gallium, a promising candidate to disrupt the vicious cycle driving osteolytic metastases, Biochem Pharmacol. 116(), 11-21

I. Strazic Geljic, N. Melis, F. Boukhechba, S. Schaub, C. Mellier, P. Janvier, J.P. Laugier, J.M. Bouler, E. Verron, J.C. Scimeca (2017). Gallium enhances reconstructive properties of a calcium phosphate bone biomaterial, J Tissue Eng Regen Med. doi: 10.1002/term.2396(),

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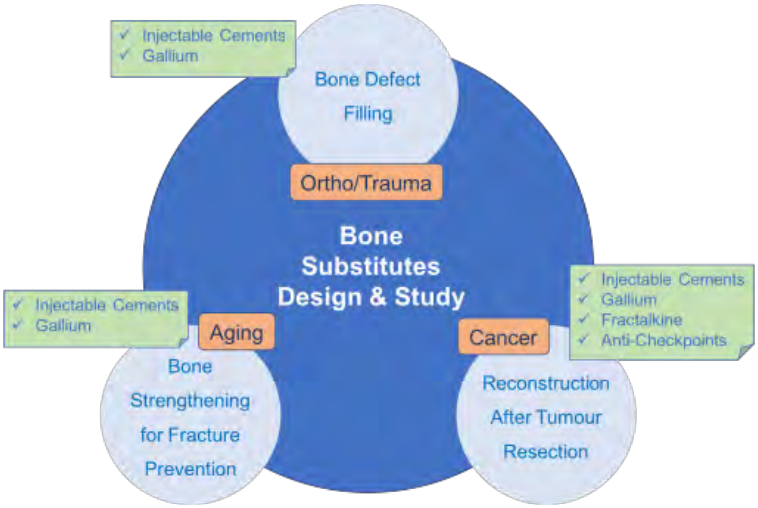
Research Themes



Bone defect filling in the course of ortho/trauma surgery - Bone reconstruction after tumour resection - Osteoporotic bone strengthening for fracture prevention.

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Claudine Blin

Osteoimmunology, niches and inflammation

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Key facts

Team

• Researchers : 4
• Technicians : 1
• Postdoc fellows : 1
• PhD Students : 2

Translational approaches

• Patents : 0
• Clinical research grants : 2
• Industry partnerships : 1

Keywords

• Osteoimmunology
• Inflammatory bone destruction
• Rheumatic diseases, osteoporosis
• Inflammation
• Hematopoietic niches
• iPS cells
• Cytometry
• Functional assays
• Cell culture
• Murine models

Focusing on the link between inflammation and bone destruction, our team proposes a novel vision on, not only how immune cells control bone resorption, but also on how bone cells modulate bone hemato-immuno niches as well as systemic immune responses

Research Brief :

The bone marrow is the site of bone remodeling and, differentiation of immune cells, but also a major reservoir of memory lymphocytes. Interactions between bone, immune and precursor cells are therefore permanent and their deregulation is associated with many pathologies, including chronic inflammatory diseases characterized by bone destruction. Our projects aim to dissect these interactions and to determine how they contribute to maintaining the homeostasis of the bone and immuno-hematological systems.

Axis 1: Osteoclasts inflammation.
Our work revealed that, depending on the context, osteoclasts induce immunosuppressive or inflammatory responses. Our aims are to better understand the origin and the new functions of these different osteoclasts, and to identify markers of the different subsets of osteoclasts in order to be able to target them specifically.

Axis 2: Memory T cells and their niches.
We have characterized the mechanisms by which memory Th17 lymphocytes contribute to inflammatory bone destruction in vivo. Our projects are focused on the analysis of the cellular interactions that allow these memory cells to be maintained in the bone marrow in particular by interacting with bone cells and MSCs. We are also developing new therapeutic approaches to control activation and/or elimination of pathogenic memory lymphocytes.

• **Methodologies Used :**

- Primary culture of human and murine bone cells: osteoclasts, osteoblasts, MSCs
- Functional assays to characterize immune cell responses (T cells, dendritic cells, monocytes)
- Flow cytometry for cell phenotyping (immune cells, MSCs, hematopoietic progenitor and stem cells)
- Flow cytometry and cell sorting of osteoclasts
- In vitro generation of CD4+ Th substets
- Generation of human iPS cells and their derivatives (MSCs, ...)
- Histological analysis on bone and other tissue
- Transcriptomic analysis

Publications

17. Augier S, Ciucci T, Luci C, Carle GF, Blin-Wakkach C, Wakkach A (2010). Inflammatory blood monocytes contribute to tumor development and represent a privileged target to improve host immunosurveillance, Journal of Immunol. 185(12), 7165-73

Mansour A, Anginot A, Mancini SJ, Schiff C, Carle GF, Wakkach A, Blin-Wakkach C (2011). Osteoclast activity modulates B-cell development in the bone marrow., Cell Research. 21(7), 1102-15

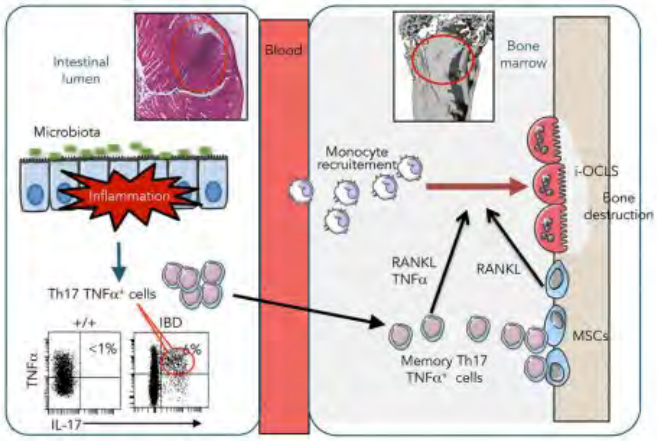
Mansour A, Abou-Ezzi G, Sitnicka E, Jacobsen SE, Wakkach A, Blin-Wakkach C (2012). Osteoclasts promote the formation of hematopoietic stem cell niches in the bone marrow, Journal of Experimental Medicine. 209(3), 537-49

Ciucci T, Ibáñez L, Boucoiran A, Birgy-Barelli E, Pène J, Abou-Ezzi G, Arab N, Rouleau M, Hébuterne X, Yssel H, Blin-Wakkach C, Wakkach A (2015). Bone marrow Th17 TNFa cells induce osteoclast differentiation, and link bone destruction to IBD, Gut. 64(7), 1072-81

Wakkach A, Rouleau M and Blin-Wakkach C. (2015). Osteoimmune interactions in inflammatory bowel disease : central role of bone marrow Th17 TNF? cells in osteoclastogenesis, Frontiers in immunology. 6(640), 1-6

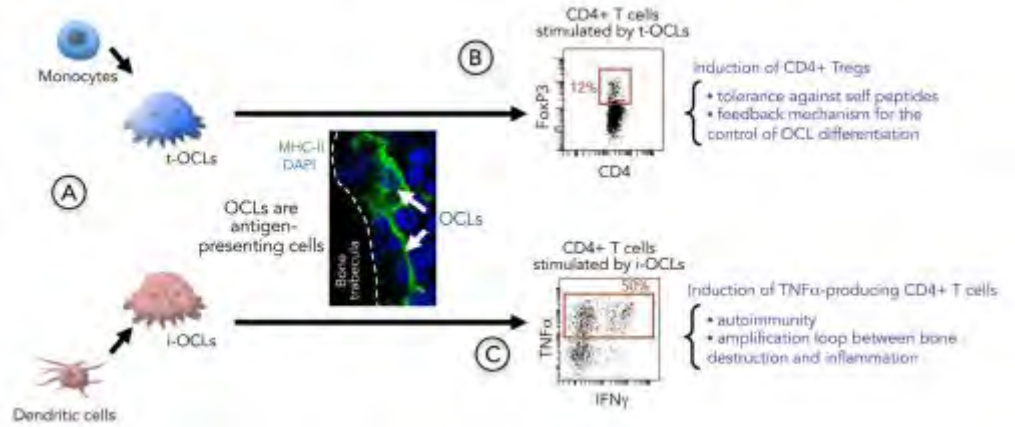
Ibáñez L, Abou-Ezzi G, Ciucci T, Amiot V, Belaïd N, Obino D, Mansour A, Rouleau M, Wakkach A, Blin-Wakkach C (2016). Inflammatory osteoclasts prime TNFa-producing CD4+ T cells and express CX3CR1, Journal of Bone and Mineral Research. 31(10), 1899?1908

Link between inflammation and bone destruction in Crohn's disease



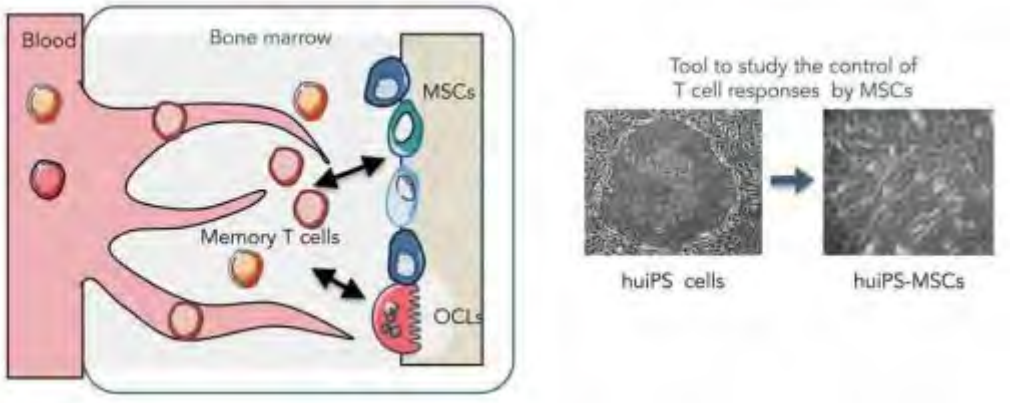
Bone destruction is a hallmark of inflammation. Gut inflammation generates TNFa-producing Th17 cells that migrate to the bone marrow where they dramatically increase osteoclast differentiation. (i) They produce osteoclastogenic factors (RANKL, TNFa), (ii) they stimulate MSCs to produce RANKL, and (iii) they increase in MSCs the expression of chemokines attracting OCL precursors (monocytes). The resulting osteoclasts have an inflammatory phenotype (i-OCLs) participating to inflammatory responses.

The immune function of osteoclasts



(A) Osteoclasts (OCLs) have different phenotypes according to their environment / origin and are antigen-presenting cells.
(B) In steady state, tolerogenic OCLs (t-OCLs) induce regulatory T cells, that can participe to the immune tolerance to avoid autoimmune reaction against self peptides issued from bone resorption.
(C) In an inflammatory context, inflammatory OCLs (i-OCLs) induce TNFa-producing CD4+ T cells that can participe to autoimmune reactions and link inflammation and bone destruction.

Interaction between memory CD4+ T cells and MSCs in the bone marrow



The bone marrow is a major reservoir for memory T cells. Maintenance of these cells in the bone marrow is controlled by bone marrow cells, in particular mesenchymal stromal cells (MSCs) and osteoclasts (OCLs). Establishment of clones of MSCs derived from induced-pluripotent stem (huiPS) cells represents an original model to study the mechanisms involved in these interactions in human in normal and pathological conditions.

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Daniel Chappard

GEROM: Research Group on Bone Remodeling and bioMaterials

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ANR LabCom UPRES EA 4658
Daniel Chappard
Angers

Key facts

Team

- Researchers : 14
- Technicians : 4
- Postdoc fellows : 0
- PhD Students : 3

Translational approaches

- Patents : 1
- Clinical research grants : 0
- Industry partnerships : 4

Keywords

- bone remodeling
- biomaterials
- bone quality
- bone microarchitecture
- bone diseases
- Raman microscopy
- microcomputed tomography
- histomorphometry
- FTIR microscopy
- nanocomputed tomography

Biological Resources

- In vivo animal models
- In vitro models

The originality of our Unit consists in a large panel of histological techniques applied to the study of bone diseases (metabolic and malignant) and the use of bone biomaterials.

Research Brief :

Bone remodeling allows the constant adaptation of the skeleton to local variations of strains, to hormonal and metabolic changes during all the life. The coordinated action of osteoclasts and osteoblasts acting in concert influence the properties of the bone mineral matrix (i.e., bone quality) and particularly the microarchitecture of bone tissue. The microarchitecture of trabecular bone can be altered in a variety of metabolic bone diseases such as osteoporosis, primary hyperparathyroidism and also when malignant cells invade the bone marrow (myeloma, lymphomas and metastasis). We have developed a number of techniques to measure bone microarchitecture on human bone biopsies and animal bone specimens. The use of new 2D stereological methods has been proposed using Euclian and fractal geometry. These techniques allowed us to characterize various types of osteoporosis with different bone microarchitecture (post-menopausal osteoporosis, glucocorticoid-induced or idiopathic male osteoporosis). The use of microcomputed tomography (microCT) was also extensively developed to analyze bone directly in 3D. The importance of microarchitecture was also evidenced in bone biomaterials where it was found to influence the migration of wear debris in prosthesis loosening. The microarchitecture of biomaterials themselves is important to consider and new biomaterials with a 3D architecture mimicking that of bone have been proposed.

Methodologies Used :

microcomputed tomography (microCT) and nanocomputed tomography
bone histomorphometry
videomicroscopy
animal models of bone diseases
FTIRI and Raman microscopy
image analysis
polymer chemistry

Publications

KÜN-DARBOIS J.D., LIBOUBAN H., CHAPPARD D. (2015). Botulinum toxin in masticatory muscles of the adult rat induces bone loss at the condyle and alveolar regions of the mandible associated with a bone proliferation at a muscle enthesis., Bone. 7(), 75-82

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AGUADO E., MABILLEAU G, GOYENVALLE E., CHAPPARD D. (2017). Hypodynamia alters bone quality and trabecular microarchitecture, Calcified Tissue Int.. 100(), 332-340

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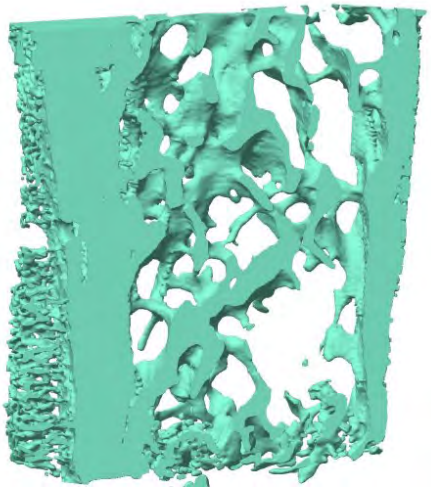
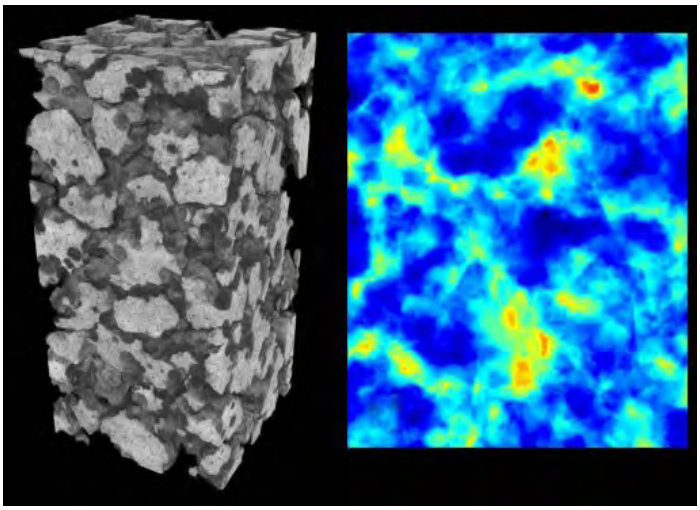
MicroCt in a case of bone metastasis in human



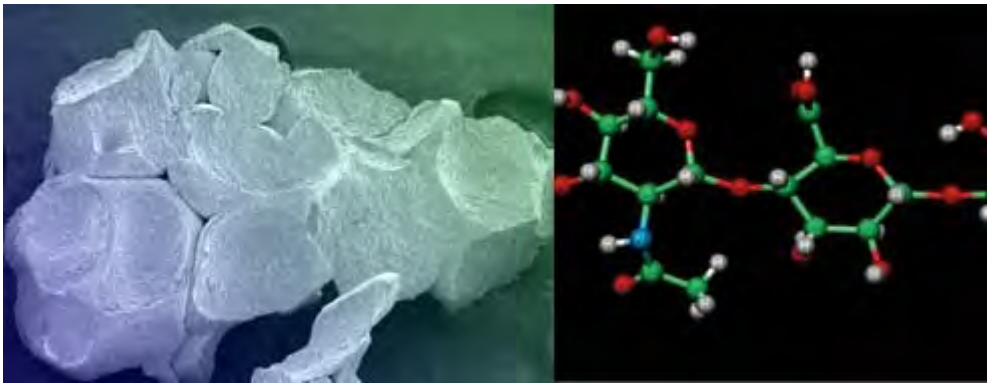
Bone biopsy imaged by microcomputed tomography. Note the irregularity of repartition of the trabeculae in the cancellous space (corresponding to focal osteolysis) and the reactive proliferation of woven bone on the periosteal side of the left cortice.

MicroCT analysis of a stack of granules of a bone substitute



MicroCT analysis of a stack of beta-tricalcium phosphate granules used as a bone substitute. Leftt: original microCT image in 3D, Right: vector analysis of this stack.

Granule of a biomaterial with hyaluronic acid



Hyaluronic acid can facilitate the handling of biomaterials. In addition, it can bind the circulating growth factors.

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Research teams with secondary association to PMN Institute

Yannick Allanore

Translational genetics in systemic sclerosis

Paris Descartes
INSERM U1016 UMR 8104
Pierre Olivier Couraud
Paris

Key facts

Team

- Researchers : 3
- Technicians : 3
- Postdoc fellows : 1
- PhD Students : 4

Translational approaches

- Patents : 1
- Clinical research grants : 10
- Industry partnerships : 8

Keywords

- Auto-immunity
- genetics

High translational applications with really from bench to bedside and back

Research Brief :

Immune-mediated diseases comprise a clinically heterogeneous group of diseases affecting about 5% of individuals of European origin. Knowledge of their pathogenic mechanisms has strikingly increased these recent years taking advantage of the huge progresses made in immunogenetics.
Our research offers a unique opportunity both in basic and in translational approaches to continue the deciphering of immunogenic disorders. Our goal is to link inflammation and immune system with human diseases based on a multidisciplinary approach which involves a two-way process going back and forth between the analysis of the genetic data, the dissection of immunological mechanisms and the potential transfer of the findings to the patient management.

• Methodologies Used :

Re sequencing
genotyping
cellular biology
molecular biology
animal models

Publications

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Ruzehaji N, Frantz C, Ponsoye M, Avouac J, Pezet S, Guilbert T, Luccarini JM, Broqua P, Junien JL, Allanore Y. (2016). Pan PPAR agonist IVA337 is effective in prevention and treatment of experimental skin fibrosis., Ann Rheum Dis. 75(12), 2175

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Frédéric Mallein-Gerin

BIOLOGY AND ENGINEERING OF CARTILAGE

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Molecular understanding of chondrocyte differentiation, construction and degradation of the cartilage matrix is used to develop multi-factorial approach combining cells, microenvironment, signaling molecules and mechanical conditioning for reconstruction of cartilage in clinical-grade conditions.

Key facts

Team

- Researchers : 6
- Technicians : 1
- Postdoc fellows : 0
- PhD Students : 2

Translational approaches

- Patents : 2
- Clinical research grants : 0
- Industry partnerships : 2

International research links

- Sweden
- USA
- Italy

Keywords

- biomaterials
- cartilage
- dental pulp
- stem cells
- tissue engineering
- human cell cultures
- animal models
- bioreactors
- immuno-histology

Biological Resources

- Pre-clinical studies in animal
- Cell biobank

Research Brief :

Cartilage is not vascularized and presents poor healing potential. Consequently, traumatic and degenerative lesions of articular cartilage eventually progress to osteoarthritis, a worldwide leading source of disability. Common surgical treatments are not satisfactory since often leading to the production of fibrocartilage, and joint replacement is a short-term therapy because knee prostheses have limited life spans. In this context, cartilage is a good candidate for developing tissue engineering procedures for its repair.
The field of regenerative medicine should be inspired by developmental processes to identify differentiation factors or signaling pathways useful for tissue regeneration. With this view, our group takes advantage of its expertise on chondrocyte differentiation and cartilage development to set up innovative protocols for cartilage repair in collaboration with industrial and medical partners. More recently, we developed new research on regeneration of the pulpodental complex. In brief, our main lines of research are :
- multi-factorial, clinical-grade approach combining cells, 3D matrix, signaling molecules and mechanical conditioning for cartilage reconstruction.
- Identification of epigenetic marks of the osteoarthritic chondrocyte phenotype.
- Advanced characterization of human mesenchymal stem cells after expansion and chondrogenic commitment in hydrogel under serum-free conditions.
- Pathophysiology and regeneration of the pulpodental complex.

- **Methodologies Used :**

- 3D cell cultures of human chondrocytes
- Cell culture in hypoxia
- Tissue engineering in bioreactor
- 3D bioprinting
- pre-clinical animal studies
- Flow cytometry analysis of mesenchymal stem cells isolated from bone marrow, adipose tissue, Wharton jelly and dental pulp

Publications

Bougault C, Paumier A, Aubert-Foucher E, Mallein-Gerin F. (2009). Investigating conversion of mechanical force into biochemical signaling in three-dimensional chondrocyte cultures, Nat. prot.. 4(), 928-938

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Mayer N, Lopa S, Talo G, Lovati AB, Pasdeloup M, Riboldi S, Moretti M, Mallein-Gerin F. (2016). Interstitial perfusion culture with specific soluble factors ihibits type I collagen production from human osteoarthritic chondrocytes in clinical-grade collagen sponges, PLoS One. 11(), e0161479

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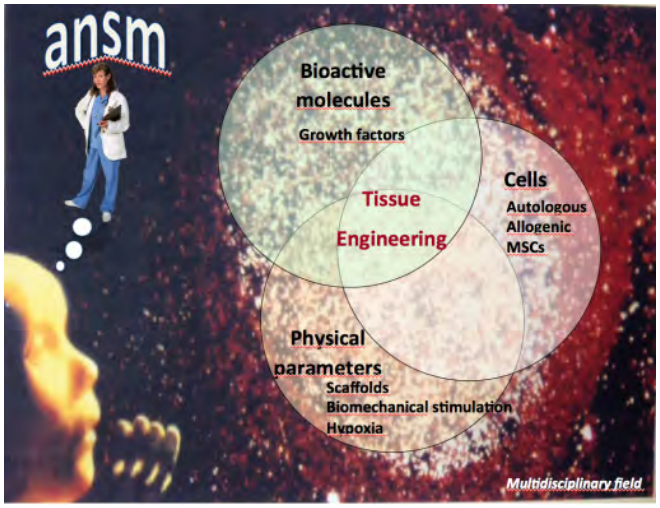
Tissue Engineering of Cartilage

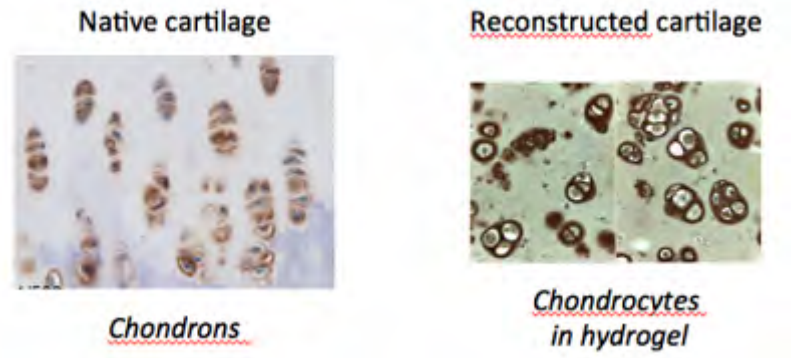


We develop innovative protocols to engineer cartilage. We explore if mesenchymal stem cells can be used as an alternative to chondrocytes and if physical parameters like mechanical forces or hypoxia can be added in the protocols. We use drug forms of soluble factors and biomaterials that are approved as medical devices.

Construction of Human Cartilage in Bioreactor

We have shown that perfusion improves the quality of the cartilage matrix synthesized by human chondrocytes seeded in clinical-grade collagen sponges. The bioreactor is an oscillating perfusion bioreactor which offers the control of several interesting parameters for optimizing the cell culture conditions.

Cartilage Matrix Reloaded in Hydrogel



In native articular cartilage, chondrocytes organize in chondrons where cells share their extracellular matrix fo form primary tissue units. By using specific combination of soluble factors: a cocktail of FGF-2/Insulin to amplify the chondrocytes then a cocktail of BMP-2/Insulin/T3 to redifferentiate the chondrocytes, it is possible to recapitulate construction of chondrons and cartilage matrix in hydrogel. This cartilage gel can then be implanted by arthroscopy to fill a cartilage defect.

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BioS EA 4691
Biomateriaux et Inflammation en Site Osseux

Sophie Gangloff

Biomatériaux et inflammation en site osseux

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Our multidisciplinary teams cover the whole spectrum of bone bioengineering coming from biomaterials synthesis through in vivo assessment with a particuar emphasis on bone loss-related pathologies.

Key facts

Team

- Researchers : 16
- Technicians : 8
- Postdoc fellows : 1
- PhD Students : 8

Translational approaches

- Patents : 3
- Clinical research grants : 0
- Industry partnerships : 5

Keywords

- Bone
- Bioengineering
- Inflammation
- Infection
- Biomaterials
- 3D scaffolds synthesis
- Stem cells
- Bone cells differentiation
- In vivo
- Bacterial biofilms

Research Brief :

The laboratory «Biomaterials and inflammation in bone site» brings together faculty and hospital practitioners (Dental surgeons - Pharmacists - Biologists) and INSERM researcher. The multidisciplinary research project aims to develop new functionalized biomatrices intended for bone filling and to evaluate their regenerative potential during interactions between host cells and biomatrices in inflammatory and/or septic environment.
To achieve these objectives, the laboratory conducted a basic research: 1) to improve the physicochemical potential of biomatrices to optimize their cellularization and their functionalization, 2) to characterize biological processes (inflammation, infection, tissue neoformation...) affecting the regenerative capacities of biomatrices and cellular immunomodulation, 3) to study the pathophysiology of bone in the context of cystic fibrosis.
Our objectives also relate to technological and methodological developments: 1) evaluation of the biocompatibility of new treatments such as superficial nanocrystallization (SMAT process) to reduce the production of articular prosthesis wear debris; 2) validation of cold plasma sterilization adapted to pre-packaged medical devices.

• Methodologies Used :

In vitro: primary human cells and/or bacteria ; Biocompatibility ; Stem cell commitment ; Inflammatory or anti-inflammatory potential ; Degradation (kinetics, particles) ; Anti-bacterial activity ; Bacterial / biofilm adhesion ; Cells / bacteria / biomaterials Interactions
In vivo: Inflammation / infection (mice) ; Air pouch model ; LPS model (IV / IP) ; Infection models Repair / bone regeneration (mice / rat) ; Femoral condyle drill defect model in mice ; Masquelet induced-membrane model in rats

Publications

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