l'institut du thorax

RESEARCH UNIT

ACTIVITY REPORT 2017-2018

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l'institut du thorax

RESEARCH UNIT

ACTIVITY REPORT 2017-2018

INSERM UMR 1087 / CNRS UMR 6291

NANTES, FRANCE

Inserm cnrs UNIVERSITÉ DE NANTES

IN PARTNERSHIP WITH

CENTRE HOSPITALIER UNIVERSITAIRE DE NANTES

“A key component of our success comes from constant partnerships between clinicians and scientists working on translational programs at l'institut du thorax.”

EDITORIAL

Created in 1996 under the leadership of Denis Escande and Hervé Le Marec, our laboratory has been recognized as a joint research unit by the Inserm and the University of Nantes since 2000. In 2004, it became the research laboratory of ***l'institut du thorax***, a highly qualified public center based at the University-Hospital of Nantes (CHU of Nantes) devoted to patient care, research and training in cardiovascular, respiratory and metabolic diseases. Our lab has continuously grown from 15 people in 1996 to about 160 today and has also been accredited by the CNRS since 2012. This steady development illustrates our capability to promote research careers and to attract brilliant scientists from France and abroad.

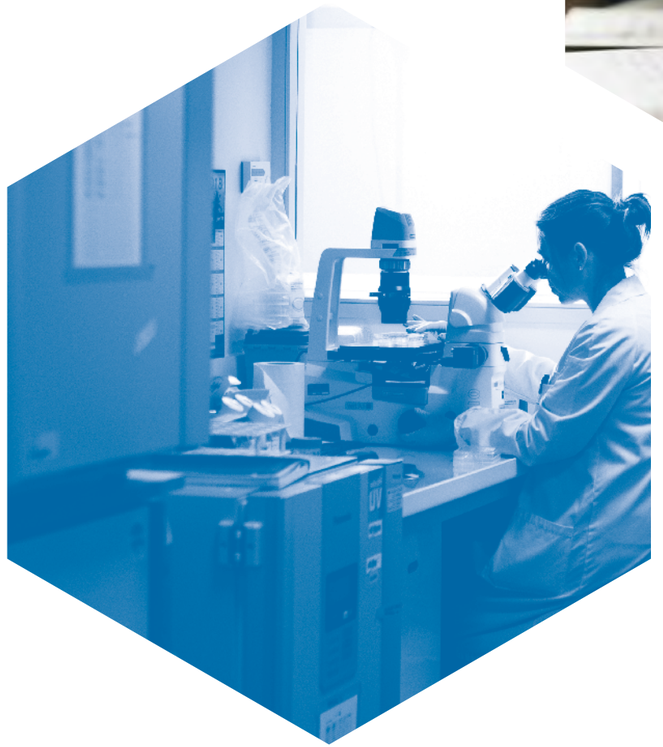
We initially conducted research on two main themes: inherited cardiac arrhythmias and vascular signaling. Through targeted recruitments, we then strengthened our skills in genomics and bioinformatics and developed additional research programs against cardiovascular, metabolic and respiratory diseases, focusing mostly on chronic conditions.

A key component of our success comes from constant partnerships between clinicians and scientists working on translational programs at ***l'institut du thorax***. While improving basic knowledge on the pathophysiology of cardiovascular diseases, we constantly translate our research discoveries to healthcare in tight collaboration with the teams of the CHU of Nantes. Accordingly, each of our teams, while developing its own basic research, is regularly solicited to contribute to integrated research programs aiming to identify new risk markers and/or therapeutic targets. This strategy has been a cornerstone of our translational programs, positioning ***l'institut du thorax*** as key center in cardiovascular research.

We are proud to manage such a dynamic research unit, and hope that this activity report 2017-2018 will help convincing you that ***l'institut du thorax*** is the place to be for investigators willing to contribute in better understanding, preventing and curing cardiovascular, metabolic and respiratory diseases.

RICHARD REDON
DIRECTOR

GERVAISE LOIRAND
DEPUTY DIRECTOR



GENERAL PRESENTATION

L'INSTITUT DU THORAX
RESEARCH UNIT

RESEARCH UNIT
INSERM UMR 1087 / CNRS UMR 6291

RICHARD REDON, DIRECTOR
GERVAISE LOIRAND, DEPUTY DIRECTOR

GOVERNANCE

STRATEGIC COMMITTEE

LABORATORY COUNCIL

SUPPORT SERVICES

ADMINISTRATION & FINANCES
ISABELLE RIVAUD

LAB MANAGEMENT
MARTINE LE CUNFF

SCIENTIFICS AFFAIRS
STÉPHANIE CHATEL

QUALITY MANAGEMENT HEALTH & SAFETY
LESLIE AUDIGANE

RESEARCH TEAMS

TEAM I : CARDIOVASCULAR GENETICS
JEAN-JACQUES SCHOTT

TEAM II-A : ION CHANNELS AND CARDIAC ARRHYTHMIAS
FLAVIEN CHARPENTIER

TEAM II-B : HEART FAILURE AND PHARMACOLOGICAL APPROACHES
MICHEL DE WAARD

TEAM III : SIGNALING IN VASCULAR AND PULMONARY PATHOPHYSIOLOGY
GERVAISE LOIRAND

TEAM IV : DYSLIPIDEMIA AND LIPOTOXICITY
BERTRAND CARIOU

TEAM V (ATIP-AVENIR) : MITOCHONDRIAL DIURNAL RHYTHMS AND METABOLIC DISEASES
DAVID JACOBI

EMERGING TEAM : MEDICAL GENETICS
STÉPHANE BEZIEAU

CORE FACILITIES

GENOBIRD
RICHARD REDON
SOLENA LE SCOUARNEC

THERASSAY
FLAVIEN CHARPENTIER

KEY FIGURES

172 PUBLICATIONS

64 SCIENTISTS

160 MEMBERS

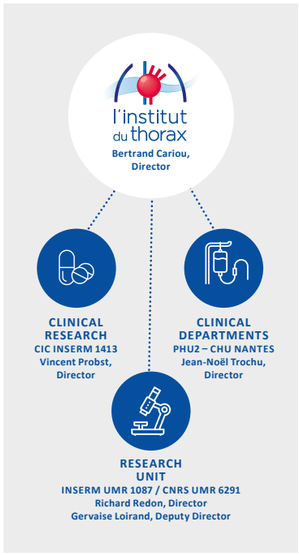
6 PATENTS APPLICATIONS

5.4 M€ FROM PUBLIC AND PRIVATE FUNDERS

18 THESES DEFENDED

GENERAL PRESENTATION_THE LABORATORY AND ITS ENVIRONMENT

THE LABORATORY AND ITS ENVIRONMENT



L'INSTITUT DU THORAX

INSERM, CNRS, UNIVERSITY OF NANTES, CHU OF NANTES

L'institut du thorax is a translational research structure dedicated to cardiac, vascular, metabolic and respiratory diseases. With a workforce of 800 people, it is organized into six clinical departments, one national reference centre for rare diseases, one centre for clinical investigations, and our research unit.

Under the leadership of Bertrand Cariou, *l'institut du thorax* combines basic research, translational programs, clinical activity, and advanced training in a single organization where clinicians and scientists cross their expertise to foster excellence and innovation through multidisciplinary programs and provide patients with state-of-the-art treatments.
Within *l'institut du thorax,* our research unit develops basic and preclinical research in close connection with the CIC-thorax, a thematic subunit in the Centre of Clinical Investigations (CIC Inserm 1413) at the CHU of Nantes. As part of their missions, CIC teams coordinate bio-banking activities — which are essential for our preclinical research — in partnership with the Centre for Biological Resources of the CHU of Nantes.

Genavie

Genavie is a corporate foundation established in December 2006 aiming to support the basic and translational research programs conducted at *l'institut du thorax*. Genavie is an extremely valuable instrument for all teams in our laboratory providing financial support for initiating new scientific programs, structuring integrated care-research projects, helping young talents and new teams to set up their research or supporting scientific careers of young investigators.

www.fondation-entreprise-genavie.org

THE FEDERATIVE RESEARCH STRUCTURE FRANÇOIS BONAMY

Our laboratory is hosted at the IRS-UN, a research building owned by the University of Nantes and located on the main site of the University-Hospital in the city centre of Nantes. We currently occupy 2,300 m^2 of wet and dry labs and develop our research activities in strong cooperation with other research units in the field of biomedical research. Technological core facilities, which are major tools in biomedical research, rely on major investments and specific scientific expertise. To promote such infrastructures, more than 15 years ago, the laboratories in Nantes decided to share their facilities through a unique federative research structure (SFR). Today, the SFR François Bonamy (Inserm UMS 016 / CNRS UMS 3556), led by Patricia Lemarchand, coordinates 20 technological facilities, all located onsite. These facilities, despite being driven by scientists from the research units, develop a policy of open access under the common rules provided by the SFR. As active members of the SFR, which is the main interlocutor of our host institutions regarding major technological investments, we manage two of these technological facilities, in genomics & bioinformatics (GenoBiRD) and physiological explorations (Therassay).

CROSSCUTTING PROGRAMS

L'institut du thorax combines basic research and translational programs to better understand the pathophysiology of cardiac, vascular, metabolic and respiratory diseases, and to identify biomarkers and therapeutic targets towards better prevention and patient care. Our research relies on tight collaboration between physicians, geneticists, computer scientists and physiologists. Such strategy has led to major breakthroughs for the last years in terms of biological resources, innovative technological approaches, and molecular mechanisms underlying diseases ◆

PREGO, THE HERITAGE DNA BANK

RFI VACARME
2013-2018: 3.4 M€ — **COORDINATORS:** H. LE MAREC & R. REDON

Between 2013 and 2018, our laboratory benefited from **an ambitious program funded by the Regional Council of Pays-de-la-Loire, VaCaRMe, which aimed at further structuring our research in genetic epidemiology and pathophysiology.**

VaCaRMe was instrumental to develop analytical models in genetic epidemiology, and to characterize the fine genetic structure of the historic populations in western France. It led to the construction of a DNA bank (PREGO) including over 5,700 individuals from the rural, sedentary population of western France (Pays-de-la-Loire and Brittany), in partnership with the French blood agency (*Établissement Français du sang*).

The program also supported genome-wide genotyping of the whole PREGO population as well as whole genome sequencing of 400 hundred individuals to impute rare alleles. Data interpretation is still in progress in our Team I (J-.J. Schott) in the context of the LabEx GenMed, in partnership with the laboratories led by J.-F. Deleuze (CEA-CNRGH, Evry) and E. Génin (Inserm UMR 1078, Brest). This new resource is an exceptional ground on which we are developing our programs in medical genetics, aiming to identify the genetic architecture of chronic diseases such as arrhythmia disorders, valvular heart diseases, intracranial aneurysms and dyslipidemias.

These recent developments led us to participate in two pilot studies of the National Plan "France Médecine Génomique 2025", respectively on diabetes (B. Cariou) and on a reference panel for human genetics (R. Redon).

www.vacarme-project.org

AN AUTOMATED SYSTEM FOR ELECTROPHYSIOLOGY 2.0

2018: 1.6 M€ — **COORDINATOR:** M. DE WAARD

Our Team II gathers experts on the biology of ion channels, on calcium homeostasis, and on drug discovery based on specific targets and phenotypes. For the last two-year period, we have made significant efforts to collect funds and purchase an **automated high-throughput patch clamp system** (*see picture on the left*) and accessory equipment for its optimal use. This cutting-edge equipment reinforces our research in electrophysiology and pharmacology, as a unique setting within the European academic environment.

This operation will greatly facilitate the development of key research programs aiming to:

- **Better understand the dysfunction in Ca^{2+} homeostasis in human cardiomyocytes** derived from iPS cells in the context of catecholaminergic polymorphic ventricular tachycardia (CPVT),
- **Screen animal venoms** for new active peptides on leading cardiac ion channels,
- **Test tertiapin Q**, a bee venom peptide, for the treatment of bradycardia and sinus node dysfunction,
- **Test the impact** of the numerous **phosphorylation sites** of the cardiac sodium channel $Na_v1.5$ identified using an unbiased and comprehensive phosphoproteomic approach on its function,
- **Characterize the functional effect of all reported genetic variations on the human hERG ($K_v11.1$) channel** in order to build a public web-accessible anonymous database providing diagnostic and prognostic information in the context of cardiac hERG-related channelopathies, and exhaustive knowledge on the structure/function relationships of the channel, which will be useful in designing new channel modulators and assessing cardiac safety of new drugs.

NEW INSIGHTS IN THE PATHOPHYSIOLOGY OF INTRACRANIAL ANEURYSMS

BOURCIER R ET AL., *AM J HUM GENET.* 2018; 102(1): 133-141

2015-2019: 740K€
COORDINATORS: H. DESAL, R. BOURCIER, G. LOIRAND

Intracranial aneurysms (IAs) are acquired cerebrovascular abnormalities characterized by localized dilation and wall thinning in intracranial arteries, possibly leading to subarachnoid hemorrhage and severe outcome in case of rupture. We have recently set up a **translational program aiming to better understand the pathophysiology of IA by determining the clinical, biological, genetic and imaging factors that can favour its formation**. Our research on IA relies on a tight partnership between our Teams I (J.-J. Schott) and III (G. Loirand) and the Department of Interventional Neuroradiology at the University-Hospital of Nantes (H. Desal). This research, initially supported by VaCaRMe, has rapidly developed into a nationwide collaborative network, (ICAN), funded by the ANR (French Ministry of Research) and the DGOS (French Ministry of Health). ICAN has already recruited more than 2,800 index cases with typical IA in less than 4 years, and has been a unique opportunity to build multidisciplinary collaboration between neuroradiologists, neurologists, neurosurgeons, geneticists, cardiologists, ophthalmologists, vascular specialists, computer scientists and biologists.

ICAN has already enabled us to discover a new susceptibility gene for IA formation in familial forms of the disease.
Indeed, we identified a rare nonsense variant (c.1378A>T) located in the last exon of *ANGPTL6* (Angiopoietin-Like 6), which encodes a circulating pro-angiogenic factor mainly secreted from the liver in a large pedigree with multiple IA-affected case subjects. We demonstrated that this variant leads to the expression of a truncated form of ANGPTL6 that is not secreted but retained in the cytoplasm. In agreement with this result, we showed a 50% reduction of ANGPTL6 serum concentration in individuals heterozygous for the variant compared to relatives homozygous for the normal allele. Sequencing *ANGPTL6* in a series of 94 additional IA index cases detected a significant enrichment in rare coding variants compared to a reference population of 404 individuals with French ancestry. Understanding why this *ANGPTL6* variant promotes IA formation opens new perspectives towards deciphering the pathophysiological mechanisms underlying IA formation. To this end, we have generated a mouse model expressing this variant that we are currently characterizing.

RHU CHOPIN: TOWARDS PRECISION MEDICINE IN HYPERCHOLESTEROLEMIA

2016-2021 : 8.3 M€
COORDINATOR: B. CARIOU

Based on a multidisciplinary public-private national consortium involving 15 teams specialized in dyslipidemias, **CHOPIN (CHOlesterol Personalized Innovation) is a translational project aiming to identify new markers of cardiovascular risk and new targets of LDL-C metabolism towards implementing personalized management of hypercholesterolemia.** CHOPIN capitalizes on large clinical cohorts of familial cases with both genetically high or low LDL-C levels and relies on cutting-edge infrastructures in genomics, bioinformatics, lipidomics and metabolomics (Team I, J.-J. Schott and Team IV, B. Cariou).

CHOPIN is organized in four research axes to:

- **Address the biology of PCSK9** — an established therapeutic target for hypercholesterolemia – with a specific focus on its role in post-prandial lipemia, Lp(a) metabolism, pancreatic ß-cell function and cell differentiation.
- **Develop a cohort of patients with familial hypercholesterolemia (FH) without atherosclerotic lesions,** in order to: (i) identify new genes and biomarkers modulating the cardiovascular risk among FH patients, (ii) decipher the molecular mechanism(s) underlying cardiovascular protection in this high-risk population, and (iii) screen for therapeutic targets in this clinical context.
- **Assess the long-term safety of low LDL-C concentrations** by following up subjects with familial hypobetalipoproteinemia (FHBL). Genotype-phenotype correlations in FHBL should give new insights into the safety of novel drug targets.
- **Investigate new genes involved in LDL-C metabolism** and thus potentially new drug targets. Whole genome sequencing combined with linkage analysis is performed in large families with unexplained FH or FHBL. The hiPSC-derived hepatocyte model is then used to investigate the function of the new identified genes.

CHOPIN should enable to identify those patients most at risk of cardiovascular disease and provide them with the best possible therapeutic strategies.

www.rhuchopin.fr

OUR TRANSDISCIPLINARY PARTNERSHIPS IN NExT

Biomedical research has fundamentally changed over the past decade, with unprecedented capability to produce huge amounts of biological data on bench-top instruments. To address this 'big data' issue, *l'institut du thorax* has built collaborative programs with researchers from other disciplines. Transdisciplinary research is increasingly developing in our lab with the strong support from the I-SITE NExT.

Firstly, we have developed strong collaboration with the Team ComBi (Combinatorics and Bioinformatics) of the Laboratory of Digital Sciences of Nantes (LS2N). ComBi develops methods, models and algorithms to study problems arising in genomics, metagenomics and systems biology. In this context, under the co-leadership of ComBi and our Team I (J.-J. Schott), the bioinformatics core facility of Nantes (BiRD) has now developed into a shared R&D facility between biologists and computer scientists. This partnership is a key component of the integrated research cluster **SysMics**, recently funded by NExT. Relying on the GenoBiRD infrastructure, SysMics aims at federating the scientific community in Nantes toward a common objective: **anticipate the emergence of systems medicine by developing approaches in population-scale genomics.** Our objective is to build a full infrastructure in Systems Medicine to accelerate the discovery and validation of biomarkers/therapeutic targets in the fields of excellence of NExT, including cardiovascular research.

Secondly, the identification of new pharmacological targets by our teams naturally opens up to the development of ligands/inhibitors of these targets. In this context, our Team IIb (M. De Waard) and Team III (G. Loirand) has set up collaborative research with medicinal and computational chemists from the **Ceisam** (CNRS UMR 6230, Nantes) and the **UFIP** (CNRS UMR 6286, Nantes). These programs funded by the regional council of Pays-de-la-Loire (**Piramid**) and NExT (**Tropic**) aim to model and synthetize innovative drugs.

Thirdly, *l'institut du thorax* participates to emerging projects in social sciences and humanities aiming to evaluate the societal impact of biomedical research in the era of genomics and personalized medicine, in collaboration with **Catherine Bourgain (Cermes3, Villejuif)** and **Stéphane Tirard (Centre François Viète, Nantes)**. Particular emphasis is placed on the interface between biomedical research and medical practice through the recent history of molecular biology on the one hand, and on the complex relationship between the concept of personalized medicine and the exploitation of big data on the other hand.

For the next three years, our research activity will further benefit from the resources implemented by VaCaRMe and by I-SITE NExT. We will further develop research in genomics applied to cardiovascular diseases in conjunction with programs in pathophysiology, thus exploiting each of our genetic discoveries through innovative approaches such as cell models directly derived from the patient through the iPS cell technology. While pursuing the development of our state-of-the-art core facilities in genomics, bioinformatics and functional explorations, we aim at contributing to the emergence of a new core facility dedicated to bio-imaging in translational research, in connection with the SFR François Bonamy, in order to promote new translational programs based on large-scale genotype-phenotype correlations.

NExT

NExT — the I-SITE (Initiatives Sciences, Innovation, Territories, Economies) in Nantes is the result of a call for a project launched by the French government to promote the emergence of a university with worldclass scientific power in Health and Engineering (60 M€). This program represents a unique opportunity to develop interactions, attract new people and researchers and strengthen the link with the private sector. Eight I-SITE projects were selected including NExT in Nantes. The implementation of the project is part of a strengthened collaboration between the institutional founders (University of Nantes, Centrale Nantes, CHU of Nantes and Inserm) and the partners (CNRS, IFSTTAR, INRA, ICO, ITM Atlantic, ONIRIS).

next-isite.fr

MAJOR PUBLICATIONS

AS FIRST, LAST AND/OR CORRESPONDING AUTHORS.

2017

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

Derangeon* M, Montnach* J, Cerpa CO, Jagu B, Patin J, Toumaniantz G, Girardeau A, Huang CLH, Colledge WH, Grace AA, Baró I, Charpentier F.
Transforming growth factor β receptor inhibition prevents ventricular fibrosis in a mouse model of progressive cardiac conduction disease. *Cardiovasc Res* 113: 464–474, 2017.

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Familial Catecholamine-Induced QT Prolongation in Unexplained Sudden Cardiac Death. *J Am Coll Cardiol* 69: 1642–1643, 2017.

Joubert M, Jagu B, Montaigne D, Marechal X, Tesse A, Ayer A, Dollet L, Le May C, Toumaniantz G, Manrique A, Charpentier F, Staels B, Magré J, Cariou B, Prieur X.
The Sodium-Glucose Cotransporter 2 Inhibitor Dapagliflozin Prevents Cardiomyopathy in a Diabetic Lipodystrophic Mouse Model. *Diabetes* 66: 1030–1040, 2017.

Pain M, Royer P-J, Loy J, Girardeau A, Tissot A, Lacoste P, Roux A, Reynaud-Gaubert M, Kessler R, Mussot S, Dromer C, Brugière O, Mornex J-F, Guillemain R, Dahan M, Knoop C, Botturi K, Pison C, Danger R, Brouard S, Magnan A, COLT Consortium.
T Cells Promote Bronchial Epithelial Cell Secretion of Matrix Metalloproteinase-9 via a C-C Chemokine Receptor Type 2 Pathway: Implications for Chronic Lung Allograft Dysfunction. *Am J Transplant* 17: 1502–1514, 2017.

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Progressive Atrial Conduction Defects Associated With Bone Malformation Caused by a Connexin-45 Mutation. *J Am Coll Cardiol* 70: 358–370, 2017.

2018

André-Grégoire G, Dilasser F, Chesné J, Braza F, Magnan A, Loirand G, Sauzeau V.
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Baruteau A-E, Kyndt F, Behr ER, Vink AS, Lachaud M, Joong A, Schott J-J, Horie M, Denjoy I, Crotti L, Shimizu W, Bos JM, Stephenson EA, Wong L, Abrams DJ, Davis AM, Winbo A, Dubin AM, Sanatani S, Liberman L, Kaski JP, Rudic B, Kwok SY, Rieubland C, Tfelt-Hansen J, Van Hare GF, Guyomarc'h-Delasalle B, Blom NA, Wijeyeratne YD, Gourraud J-B, Le Marec H, Ozawa J, Fressart V, Lupoglazoff J-M, Dagradi F, Spazzolini C, Aiba T, Tester DJ, Zahavich LA, Beauséjour-Ladouceur V, Jadhav M, Skinner JR, Franciosi S, Krahn AD, Abdelsayed M, Ruben PC, Yung T-C, Ackerman MJ, Wilde AA, Schwartz PJ, Probst V.
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Bourcier R, Le Scouarnec S, Bonnaud S, Karakachoff M, Bourcereau E, Heurtebise-Chrétien S, Menguy C, Dina C, Simonet F, Moles A, Lenoble C, Lindenbaum P, Chatel S, Isidor B, Génin E, Deleuze J-F, Schott J-J, Le Marec H, ICAN Study Group, Loirand* G, Desal* H, Redon* R.
Rare Coding Variants in ANGPTL6 Are Associated with Familial Forms of Intracranial Aneurysm. *Am J Hum Genet* 102: 133–141, 2018.

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Roux-en-Y gastric bypass reduces plasma cholesterol in diet-induced obese mice by affecting trans-intestinal cholesterol excretion and intestinal cholesterol absorption. *Int J Obes (Lond) 42:* 552–560, 2018.

AWARDS

FRANÇOIS PETAY AWARD – FONDATION POUR LA RECHERCHE MÉDICALE : ANTOINE MAGNAN

NOVEMBER 2018

"AUGUSTE LOUBATIÈRES AWARD" 2017 – SOCIÉTÉ FRANCOPHONE DU DIABÈTE BERTRAND CARIOU

LDL CHOLESTÉROL ET DIABÈTE : NOUVELLES CIBLES – NOUVEAUX ENJEUX

MARCH 2017

PATENTS

2017

Inhibitors of rac1 and uses thereof for inducing bronchodilatation
Inventors: Sauzeau V., Loirand G., Lebreton J., Tessier A., Quemener A.
Publication number: EP17305662
WO/2018/224560

Inhibitors of rac1 and uses thereof for treating cancers
Inventors : Sauzeau V., Loirand G., Lebreton J., Tessier A., Quemener A.
Publication number: EP17305664
WO/2018/224563

Methods and pharmaceutical compositions for modulating stem cells proliferation or differentiation
Inventors: Si Tayeb K., Idriss S., Cariou B., Roudaut M., Le May C., Caillaud A.
Publication number: WO/2018/087391

Methods and compositions for predicting and treating intracranial aneurysm
Inventors: Redon R., Loirand G., Desal H., Bourcier R.
Application number : EP17306466.8
International application number : PCT/EP2018/078947

2018

Method and composition for the treatment of allergic asthma
Inventors : Bouchaud G., Klein M., Magnan A., Colas L.
Application number : EP18305231.5

Methods and compositions for treating asthma and allergic diseases
Inventors : Cariou B., Le May C., Magnan A., Bouchaud G.
Application number : EP18306169.6

Method for locating and characterizing bifurcations of a cerebral vascular tree, associated methods and devices
Inventors : Autrusseau F., Nouri A., Bourcier R.
Application number : EP18306612.5

EXECUTIVE MANAGEMENT

Richard Redon (the Director) and Gervaise Loirand (the Deputy Director) are responsible for overall laboratory management during the contract 2017-2021, with the support of four services ◆

RICHARD REDON
PhD, Research Director, Inserm

Richard Redon is a human geneticist recognized as an international expert in the analysis of structural variation in the human genome. After his PhD on cancer cytogenetics (2002, University of Strasbourg, FR) during which he received the Young investigator Award 2002 from the European Society of Human Genetics, he joined the Wellcome Trust Sanger Institute where he contributed, as a junior postdoctoral fellow, to the development of approaches based on microarray analysis to address the role of copy number variation in evolution and disease. He joined *l'institut du thorax* in 2009 to set up his own team on the genetics of cardiac arrhythmia disorders, with the support of the ATIP-Avenir program. Since then, he has been leading international genome-wide association studies aiming to identify genetic risk factors for sudden cardiac death. Since 2013, he has also been coordinating the VaCaRMe program with Hervé Le Marec, whom he succeeded as Director of the research unit of *l'institut du thorax* in January 2017.

GOVERNANCE

To manage the laboratory, the executive team relies on two complementary instances.

Strategic committee
The teams' research activities are regularly reviewed during monthly meetings of our strategic committee, which includes the director, deputy director and team leaders in the presence of the heads of the 4 support services. The committee discusses and arbitrates on every issue affecting the life of the unit, from infrastructure investments, human resources and laboratory management to strategic opportunities.

Laboratory council
This second instance meets 3 times a year. It is composed of 15 elected staff members. During each session, the representatives deliberate with the director and the deputy director on a list of issues communicated by the staff or by the executive team.

The strategy of the laboratory is openly discussed at least once a year during a plenary scientific assembly involving all the investigators of the unit. This committee opens with presentations from the director and the central services, which is followed by discussions on specific topics.

The internal communication is organized collectively by the 4 support services. Regular information is distributed through a bi-monthly electronic newsletter to all staff members.

Scientific Advisory Board
In order to get an external assessment of the strategy of our research unit, the strategic committee will constitute an external Scientific Advisory Board (SAB), which will meet in our laboratory at mid-term (in fall 2019). Our activities will be exposed to the board, as well as our prospects for the second half of the contract 2017-2021. The remarks and recommendations from the SAB will be extremely valuable to prepare the project 2022-2026 of our unit.

SUPPORT SERVICES

The Financial and Administrative Service, led by Isabelle Rivaud, assists the director and deputy director in their administrative tasks and duties. The service, which employs **4 administrative assistants (Aurélie Garnier, Stéphanie Lemarchand-Mindé, Corinne Mandin, Ophélie Tindilière)**, runs the budget of the research unit, ensures financial follow-up for every team, manages the human resources in close connection with the central services of the host institutions, and organizes travel and accommodation for the members of staff when necessary.

As Head of the Scientific Affairs Service, Stéphanie Chatel helps the director and deputy director in preparing scientific reports and communications, coordinating crosscutting programs, organizing internal and public scientific events on behalf of the laboratory, and organizing the promotion of our research activity toward the international scientific and medical community. She is assisted in her tasks by **Séverine Abramatic**, who is responsible for selecting the most relevant calls for grant application by our investigators, and detecting knowledge transfer opportunities in connection with the Offices of Technology Transfer of the unit institutions.

The Lab management, led by Martine Le Cunff, supervises the technical organization of our dry and wet laboratories. The service comprises **4 logistic assistants (Nathalie Cressan, Emmanuelle Criaud, Davy Halary, Marie-France Le Cunff)**.
It is in charge of establishing our purchasing policy, organizing good supplies for the laboratory, and managing our bio-banks in partnership with the Centre of Biological Resources (CRB) and CIC-Thorax Center of CHU of Nantes.

Health & Safety, and Quality Management are under the responsibility of the Director. **Leslie Audigane** assists him in these tasks, in particular by advising him on the implementation of occupational H&S rules, supervising the activities of five staff members serving as prevention assistants (**Stéphanie Bonnaud, Angélique Erraud**) or referents for BSL-2 laboratories (**Amandine Caillaud, Aurore Girardeau, Virginie Forest Choquet**), and providing the research teams with dedicated resources to improve and better track their lab activities.

RESEARCH

TEAM I

CARDIOVASCULAR GENETICS

JEAN-JACQUES SCHOTT

Team leader

Jean-Jacques SCHOTT, PhD

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TEAM I

CARDIOVASCULAR GENETICS

JEAN-JACQUES SCHOTT

JEAN-JACQUES SCHOTT
PhD, Research Director, Inserm

JJ. Schott is a geneticist specialized in cardiovascular diseases. After obtaining his PhD from the University of Strasbourg in 1996, he trained as a postdoctoral fellow at Harvard Medical School, Boston. Since his arrival in Nantes in 1999, recognition has grown for his contribution to understanding of the etiology of rare and common forms of cardiovascular disorders, with a particular emphasis on cardiac arrhythmias and cardiac valve defects. His research has been funded by multiple grants from the French National ministry of research, and two transatlantic Network of Excellence grants from the Leducq foundation: "Alliance against sudden cardiac death" and "Mitral". His achievement in cardiovascular genetics has been recognized by the Mémain-Pelletier prize from the *Académie des Sciences — Fondation de l'Institut de France*, and the *Edouard Corabœuf* prize.

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Our team aims to further elucidate the heritability of cardiovascular diseases, with a particular emphasis on cardiac arrhythmia and valve disorders. To examine the contribution of both rare and common genetic variation on disease susceptibility we apply state-of-the art multi-omic approaches to elucidate the contribution of both rare and common genetic variations on disease susceptibility. While our investigations are primarily focused on gene sequences, we now aim to address the role of regulatory regions in the non-coding portion of the genome. Our goal is to identify biological risk markers for early prevention and new targets for innovative therapies ◆

RESEARCH PROGRAMS

Biostatistics and bioinformatics in genetic epidemiology

Christian Dina and Richard Redon

We develop and implement novel tools and methods to facilitate the interpretation of genetic variation in the context of genome-wide association studies based on array and/or sequencing genotypes. In parallel, we participate in a nationwide program aiming to construct a reference panel, *France GenRef*, of whole-genome sequences with French ancestry (cf. *Crosscutting programs* p.15).

Genetics of cardiac arrhythmia disorders and sudden death

Julien Barc and Vincent Probst

Inherited primary electrical disorders are relevant models for deciphering the mechanisms leading to sudden cardiac death. We aim to uncover new mutations/genes/pathways underlying sudden cardiac death risk in selected conditions, such as Brugada syndrome and cardiac conduction defects.

Genetics and pathophysiology of cardiac valve dystrophy

Solena Le Scouarnec, Jean Mérot, Romain Capoulade and Thierry Le Tourneau

In addition to our genetic investigations on familial and isolated cases of valve dystrophy, we address whether mechanical forces targeting the mitral valve are major factors leading to disease development and progression using multi-omics approaches on transgenic rats expressing the disease as well as on derived *in vitro* cell models.

Genetics of vascular and metabolic diseases

Jean-Jacques Schott, Romain Bourcier and Hubert Desal

We recently initiated new research programs aiming to identify rare and common genetic variation associated with vascular or metabolic disorders, particularly intracranial aneurysm and hypobetalipoproteinemia (cf. *Crosscutting programs* p.16).

HIGHLIGHTS

Genetics of cardiac conduction defects

Mutations in connexin-45 cause a new syndrome with cardiac conduction disease (CCD)

Seki A et al. *J Am Coll Cardiol* 2017;70:358–370

We genetically screened 15 European cases with genotype-negative *de novo* atrioventricular (AV) block and their parents by trio whole-exome sequencing, plus 31 Japanese cases with genotype-negative familial AV block or sick sinus syndrome by targeted exon sequencing of 457 susceptibility genes. Functional consequences of the mutation were evaluated using an *in vitro* cell expression system and *in vivo* knockout mice. We identified a connexin-45 (*Cx45*) mutation (p.R75H) in 2 unrelated families (a *de novo* French case and a 3-generation Japanese family) who presented a progressive AV block resulting in atrial standstill without ventricular conduction abnormalities. Affected individuals shared a common extracardiac phenotype: a brachyfacial pattern, finger deformity, and dental dysplasia. Mutant Cx45 showed normal hemichannel assembly and plaque formation but impaired gap junction conductance suggesting a dominant-negative effect. Cardiac-specific Cx45 knockout mice showed sinus node dysfunction and atrial arrhythmia, recapitulating the intra-atrial disturbance.

Genotype-phenotype correlation and identification of higher-risk subgroups in neonates and children carrying *SCN5A* mutations

Baruteau A-E et al. *Eur Heart* J 2018;39:2879–2887

Mutations in the *SCN5A* gene encoding the alpha subunit of the cardiac sodium channel ($Na_v1.5$) cause various types of cardiac arrhythmias, conduction defects, and cardiomyopathies. Some patients with *SCN5A* mutations are predisposed to sudden cardiac death (SCD), independently of age. We conducted a large multicenter, international, retrospective cohort study in 25 tertiary hospitals in 13 countries between 1990 and 2015 and report the clinical evaluation and follow-up of a large pediatric population of *SCN5A*-mutation-positive individuals. All patients under 16 years-old and diagnosed with a genetically confirmed *SCN5A* mutation were included in the analysis. A total of 442 children from 350 families were included, of which 67.9% were asymptomatic at diagnosis. Four main phenotypes were identified: isolated progressive cardiac conduction disorders (25.6%), overlap phenotype (15.6%), isolated long QT syndrome type 3 (10.6%), and isolated Brugada syndrome type 1 (1.8%); 44.3% had a negative electrocardiogram phenotype. During a median follow-up of 5.9 (IQR 5.9) years, 272 cardiac events had occurred in 139 (31.5%) patients. Patients whose mutation localized in the C-terminus had a lower risk. Compound genotype, both gain- and loss-of-function *SCN5A* mutation, age ≤1 year at diagnosis in probands, and age ≤1 year at diagnosis in non-probands were independent predictors of cardiac events.

FLNA mutations and mitral valve dystrophy

Extensive genotype-phenotype correlations in *FLNA* families

Le Tourneau T et al. *Eur Heart J* 2018;39:1269 1277

We first investigated mitral valve dystrophy among 246 affected subjects with (n=72) or without one out of three distinct *FLNA* mutations. In this X-linked disease, valve lesions were severe in men and moderate in women. Most men presented with classical leaflets of mitral valve prolapse but no chordal rupture. In contrast to regular mitral valve prolapse, mitral leaflet motion was clearly restricted in diastole and papillary muscles position was closer to the mitral annulus. Valvular abnormalities were similar in the families, in adults and young patients from early childhood suggestive of a developmental disease. In addition, mitral valve lesions worsened over time as encountered in degenerative conditions. Polyvalvular involvement was frequent in men and non-diagnostic forms were frequent in women. Overall, survival was moderately impaired in men.

Functional characterization of a *FLNA*-P637Q knock-in rat model

Haataja TJK et al. *Structure* 2019;27:102-112.e4.

We developed a knock-in rat model harboring the *FLNA*-P637Q mutation mimicking the familial mitral valve prolapse mutation. Multimodal imaging approaches established the presence of dystrophic mitral valve and histology confirmed significantly thicker mitral valve leaflets. Using micro computed tomography and the complete 3D reconstruction of explanted heart, we showed that the volume of the mitral valve leaflets was significantly higher in the knock-in than in the control rats, confirming that these transgenic rats express similar phenotypes as observed among patients and thus are highly relevant *in vivo* models to elucidate the pathophysiology of mitral valve prolapse. Furthermore, using X-ray protein structural and molecular dynamics analysis we demonstrated that the *FLNA*-P637Q mutation, identified in familial mitral valve prolapse and encoding an actin binding protein, impedes the force resilience of this actin binding protein.

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FUNDING

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ION CHANNELS AND CARDIAC ARRHYTHMIAS

FLAVIEN CHARPENTIER

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TEAM IIA

ION CHANNELS AND CARDIAC ARRHYTHMIAS

FLAVIEN CHARPENTIER

Our objective is to decipher the function and regulation of cardiac ion channels in both physiological and pathological conditions. Our projects are mainly focused on hereditary rhythm and conduction disorders (channelopathies). ◆

FLAVIEN CHARPENTIER
PhD, Research Director, Inserm

F. Charpentier is an expert in cardiac electrophysiology, from the cellular level to the whole animal, and is mainly interested in the cellular and molecular mechanisms of inherited cardiac arrhythmic syndromes. He was awarded his PhD from the University of Nantes in 1991. He was recruited by Inserm and joined the laboratory in 1996 after a postdoctoral position at Columbia University (New York, USA). He has contributed to 74 publications (h index = 28). He has coordinated four state-funded grants, including two from the *Agence Nationale de la Recherche* (ANR), seven grants from French national foundations, and also participated as team leader in a European Union network and two ANR grants. He has been a member of evaluation committees for the ANR, Inserm-DGOS and Swiss National Research Council, and of the scientific councils of two French foundations. He is on the editorial board of three journals.

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RESEARCH PROGRAMS

Cardiac arrhythmias and sudden death

Isabelle Baró, Nathalie Gaborit

In this program, we aim to identify the pathophysiological mechanisms of inherited cardiac arrhythmias by combining molecular, cyto/histological and electrophysiological studies on cardiomyocytes generated from induced pluripotent stem cells obtained from affected patients and on knock-in mouse models. Our projects are mostly focused on the Brugada syndrome and familial catecholamine-induced QT prolongation.

Fibrosis and disorders of cardiac conduction

Flavien Charpentier

This program aims to identify therapeutic targets in the signaling pathways involved in the development of fibrosis during aging in hereditary forms of progressive cardiac conduction disease (PCCD). It is based on pharmacological studies performed on a mouse model of *SCN5A*-related PCCD and on studies aimed at identifying the role of the *SCN5A* gene product, the main cardiac sodium channel $Na_V1.5$, in cardiac fibroblasts.

Post-translational regulation of $Na_V1.5$

Céline Marionneau

In this program, our objective is to identify novel phosphorylation sites on $Na_V1.5$ and its regulatory partners using a phosphoproteomic approach performed in cardiac tissues from control and transgenic mice and to decipher the role of these sites in the post-translational regulation of $Na_V1.5$ by performing biochemical and electrophysiological studies on cardiomyocytes genetically modified with adenoviruses.

Cardiac ion channels: from biophysics to therapeutic application

Gildas Loussouarn

In this program, we seek to identify peptide sequences controlling the opening of voltage-dependent ion channels involved in cardiac channelopathies, such as $K_V7.1$ and $K_V11.1$ potassium channels, and develop therapeutic tools targeting these sites.

HIGHLIGHTS

Identification of the molecular domains involved in $K_V11.1$ potassium channel voltage-dependent opening

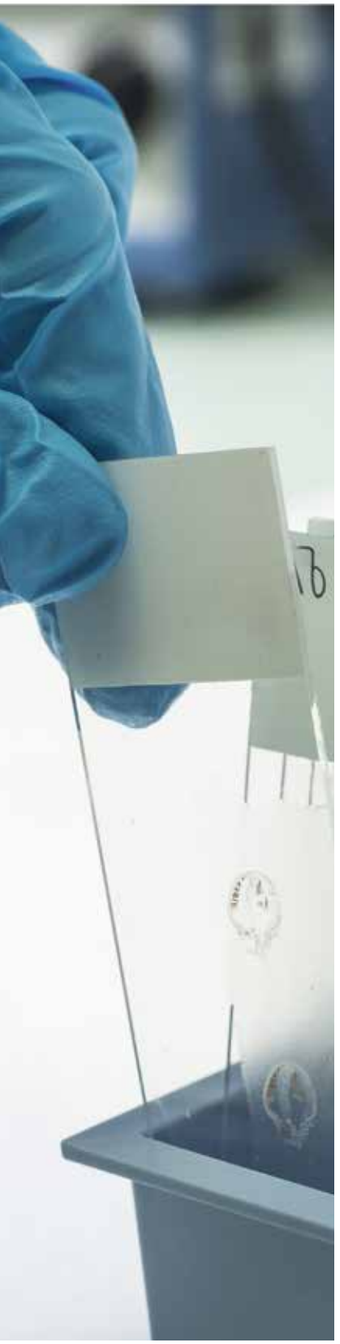
Malak O et al., *Sci Rep* 2017; 7:113

Delayed-rectifier potassium channels ($K_V11.1$ alias hERG1 and $K_V7.1$ alias KCNQ1) play a major role in cardiac repolarization. These channels are organized in a tetrameric pore (comprising the S5–S6 transmembrane segments of the four channel-forming K_V subunits) surrounded by four voltage sensor domains (formed by the S1–S4 transmembrane segments). Coupling between voltage sensor domains and the pore activation gate is critical for channel voltage-dependence. The S4–S5 linker between S1–S4 and S5–S6 regions seems to play a major role. However, it is still debated and the molecular mechanisms remain elusive. In this study, we demonstrated that covalently binding a peptide mimicking the S4–S5 linker (S4–S5L) to the channel gate represented by the S6 C–terminus (S6T), using a disulfide bridge, completely inhibited $K_V11.1$. This shows that channel S4–S5L is sufficient to stabilize the pore activation gate in its closed state. Conversely, covalently binding a peptide mimicking S6T to the channel S4–S5L prevented its inhibitory effect and rendered the channel almost voltage-independent. This shows that channel S4–S5L is necessary to stabilize the activation gate in its closed state. Altogether, our results provide chemical evidence 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 delayed rectifier potassium channels. In other studies, we have shown that such inhibiting and activating channel-specific peptides can be used to modulate cardiac $K_V7.1$ and neuronal $K_V10.2$ channels. Altogether, these studies pave the way for a new therapeutic strategy based on a general mechanism of voltage-dependence.

Identification of a role for the transcription factor IRX5 in cardiac conduction

Al Sayed ZR et al., *Submitted for publication*

Several inherited arrhythmic diseases have been linked to single gene mutations in cardiac ion channels and interacting proteins. However, the mechanisms underlying most arrhythmias involve altered expression of multiple effectors. We thus investigated the role of a transcription factor belonging to the Iroquois homeobox family, IRX5, in cardiac electrical function. Transcriptome correlative analyses between IRX5 and genes involved in cardiac electrical activity showed that in the human ventricular compartment, IRX5 expression is strongly correlated with the expression of major actors of cardiac conduction, including the sodium channel $Na_V1.5$ and the Connexin 40 (Cx40). We then generated cardiomyocytes from induced pluripotent stem cells (iPSC-CM) derived from two Hamamy Syndrome-affected patients carrying distinct homozygous loss-of-function mutations in the IRX5 gene. These iPSC-CM showed impaired cardiac expression of numerous genes including $Na_V1.5$, Cx40 and Cx43. We also identified a novel cardiac transcription factor complex made up of IRX5 and GATA4, in which IRX5 potentiated GATA4-induction of $Na_V1.5$ expression. In accordance with the prolonged QRS interval observed in Hamamy Syndrome patients, a slower ventricular action potential depolarization due to sodium current reduction was observed in the patients' iPSC-CM, confirming the functional role of IRX5 in electrical conduction. Altogether, this work reveals a key role of IRX5 in the regulation of human cardiac electrical conduction, and how the IRX5-GATA4 complex cooperatively regulates the expression of genes involved in cardiac conduction.



Identification of a new inherited arrhythmic disorder: catecholamine-induced QT prolongation

Huchet F et al., *J Am Coll Cardiol* 2017; 69: 1642-3

In young adults, sudden cardiac death (SCD) often occurs without identifiable ECG abnormalities or structural defects. In consequence, most SCD events in young adults remain unexplained and are classified in an elusive group known as idiopathic ventricular fibrillation. The main causes of SCD before the age of 40 are inherited arrhythmic diseases. Thus, the major preventive strategy is familial screening in order to identify family members at risk of SCD and proposition of specific treatment to reduce this risk. It was recently shown that after cases of unexplained SCD in young adults, diagnosis could be performed in 40% of families with a clinical screening of relatives including resting ECG, stress ECG and echocardiography complemented by a pharmacological challenge or MRI when needed. In this context, we have identified a new primary arrhythmic disease with autosomal dominant inheritance, characterized by familial idiopathic ventricular fibrillation, catecholamine-induced QT prolongation and severe clinical prognosis. The affected patients display a normal ECG under baseline conditions, but a pathological prolongation of the QT interval under adrenergic stimulation that can be unmasked by a mental stress test.

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TEAM IIB

HEART FAILURE AND PHARMACOLOGICAL APPROACHES

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Our research group gathers experts in: (i) drug discovery and design, (ii) signaling pathways, (iii) pathogenesis of ion channel function and regulation, (iv) *in vivo* investigation of cardiovascular functions, and (v) *ex vivo* models for heart diseases ◆

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M. De Waard is an expert on ion channels and in pharmacology. He obtained a PhD on the electrophysiological analysis of calcium currents from cerebellar granule cells (1991, University Aix-Marseille II, FR) followed by a four-year Postdoctoral internship on calcium channel biochemistry, functional reconstitution and recombinant expression (1992-1996, Howard Hughes Medical Institute, Dpt. of Physiology, University of Iowa, USA). Previously, laboratory director during 5 years at the Commissariat à l'Energie Atomique and team leader during 9 years at the Neuroscience Institute in Grenoble, he joined *l'institut du thorax* in 2016. He has authored or co-authored more than 230 articles in peer-reviewed journals (h index = 44). He is a recipient of several Regional and State grants and Foundations. He received Servier Young Investigator Award (1995), winner of the OSEO emergence prize for launching the biotech company Smartox, laureate of the most innovative company for the Rotary Club and the *Chambre de Commerce et d'Industrie de Grenoble.*

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RESEARCH PROGRAMS

High-throughput screening of ion channel variants

Michel De Waard, Sébastien Nicolas, Jérôme Montnach

This large program is based on our proven track of drug discovery using libraries of natural compounds (i.e. peptides derived from venoms) and target identification such as beta3 adrenergic receptor in heart failure with the preserved ejection fraction (HFpEF). Target-based screening relies on a high-throughput automated patch-clamp system (cf. *Crosscutting programs* p15). Based on phenotype-based screening, we identify natural compounds having notorious effects on blood pressure *in vivo*, modifying the ECG. We also aim to develop clinically relevant diagnosis/prognosis databases of ion channel variants by characterizing the biophysical and membrane-targeting properties of mutated ion channels. The purpose is to facilitate personalized therapy, rapid discovery and drug testing. At last, we will apply optopharmacology to improve understanding of ion channel function in the heart, by synthesizing specific fluorescent indicators of cardiac ion channels to investigate the fine mechanisms of electrical genesis and propagation in the heart.

iPS-derived cardiomyocytes for the in-depth characterization of human variants affecting calcium homeostasis

Michel Ronjat, Michel De Waard

This program aims to understand the pathophysiological bases of calcium homeostasis deregulation. Taking advantage of our expertise in calcium homeostasis, we exploit our tools derived from maurocalcin - a natural peptide active on the ryanodine receptor - to investigate how it may correct the phenotype of Catecholaminergic Polymorphic Ventricular Tachycardia.

Identifying risk biomarkers and therapeutic targets for HFpEF

Chantal Gauthier, Benjamin Lauzier, Jean-Noël Trochu

HFpEF, which currently accounts for 50% of all HF patients, has become a major clinical problem without effective treatment. Using our HFpEF animal model (beta3-receptor-overexpressing rat) and blood of patients suffering from HFpEF (cohort and biocollection under construction), our aims are to identify biomarkers and molecular targets relevant to this major cardiovascular burden.

Cardiac dysfunction in sepsis

Benjamin Lauzier, Bertrand Rozec, Michel De Waard

Septic shock is associated with acute cardiac dysfunction and a high rate of mortality. Our aim here is to identify by mass spectrometry key proteins secreted in blood in response to septic shock, which may promote cardiac dysfunction. We will also test whether the stimulation of O-GlcNAcylation at the early phase of septic shock is associated with an improvement of cardiovascular function, and a reduction in organ failure and mortality.

RESEARCH_TEAM IIB_**HEART FAILURE AND PHARMACOLOGICAL APPROACHES**_MICHEL DE WAARD

HIGHLIGHTS

Screening of animal venoms for the discovery of new compounds active on the cardiovascular system

Ciolek J et al., *in preparation*

While screening for muscarinic type 2 G protein coupled receptor ligands using a mamba snake venom, we identified a toxin that efficiently binds onto this receptor. *Ex vivo,* this peptide has impressive relaxing effects on mesenteric arteries and was confirmed *in vivo* by a long-lasting 50% reduction of the diastolic pressure. This manuscript in preparation describes the discovery of this new peptide, its sequence and synthesis, its 3D structure and the characterization of the functional effects. This first manuscript will be followed by a second on a more accurate description of the *in vivo* functional effects and assessing the signaling pathway. The objective is to decipher a new signaling mechanism for lowering the blood pressure that triggers hope for treating the third of human patients that are refractory to all treatments. As a result, a screening approach on mesenteric arteries has started to discover new compounds issued from snake venoms. We have identified two compounds so far, which are now under further investigations (sequencing, synthesis and elucidation of the pathways involved).

Neutralization of toxic components *in vivo* using DNA aptamers

El-Aziz TMA et al. *Sci Rep* 2017. 7: 7202 — Taiwe GS et al. *Molecules* 24, 2019

Neutralizing circulating toxic components is a particularly difficult task. One of the most usual ways is to raise antibodies against this compound. However, this is time consuming, costly, the drug is not always immunogenic, and it poses problems of storage. Herein, we validated a novel methodology of toxin neutralization using DNA aptamers, both *in vitro* and *in vivo.* This method is mainly based on the neutralization of the active pharmacophore of the toxin. A second manuscript has been published on this issue, taking advantage of the automated patch clamp technology and examining how aptamers modify the affinity of the toxin for its receptor. We expect that this technology is widely applicable for all kinds of substances that are life-threatening (drug abuse, accidental overdosing, poisoning). This technology may prove itself useful for neutralizing toxic endogenous compounds secreted during septic shock.

Identifying new therapeutic strategy in septic shock

Ferron M et al. submitted

Since 2010 we have acquired a strong expertise in sepsis and septic shock model. Two publications have been accepted in the last few years and two are currently submitted. Thanks to our work, we have demonstrated that O-GlcNAc stimulation is a potential therapeutic strategy at the early phase of septic shock. Positive results obtained in two different models, with three different pharmacological compounds at different age allowed building industrial collaboration (Baxter and Inflectis Bioscience). We are now using innovative technics of mass spectrometry to try to decipher those pathway or proteins of particular interest in our approach.

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TEAM III

SIGNALING IN VASCULAR AND PULMONARY PATHOPHYSIOLOGY

GERVAISE LOIRAND

GERVAISE LOIRAND
PhD, Research Director, Inserm

G. Loirand is a vascular biologist who has developed an internationally recognized expertise on vascular smooth muscle cells. After a PhD (1988, University of Bordeaux, FR) and a postdoctoral stay at the Institute of Molecular Pharmacology (1995–1998; University of Nice Sophia-Antipolis, FR), she joined the laboratory in 1999. She made a major contribution to the discovery of the role of Rho protein signaling in the pathogenesis of vascular diseases. She has authored more than 100 articles in peer-reviewed journals. Her research projects are mainly funded by the *Agence Nationale de la Recherche (ANR), Fondation pour la Recherche Médicale (Foundation for Medical Research), Fondation de France,* and Horizon 2020 research grants. She was awarded the Jean-Paul Binet Prize from the Foundation for Medical Research in 2012. She chaired the Inserm Scientific committee "Physiology and Physiopathology of Cardiac, Vascular, Pulmonary, Renal and Muscular Systems" from 2012 to 2016.

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Our overall objective is to understand the signaling mechanisms that control smooth muscle cell functions and their pathogenic dysregulation in vascular and pulmonary pathophysiology. The major goals of our research programs are to identify key proteins as potential therapeutic targets and to speed up clinical application of basic scientific breakthroughs.

Smooth muscle cells are able to acquire pathological phenotypes and functions including excessive contraction, proliferation, migration and exaggerated matrix production, via aberrant activation of the intracellular signaling pathways that control these processes. Our research projects aim at deciphering these derailed mechanisms through experimental approaches ranging from cellular and transgenic mouse models developed by the team, to studies in humans made possible by close collaboration with clinical services at CHU of Nantes ◆

RESEARCH PROGRAMS

Regulation of RhoA activity in arterial diseases and remodeling associated with aging

Gervaise Loirand

This program is particularly focused on the RhoA exchange factor Arhgef1, identified as a target of interest in hypertension, and the regulation of RhoA by phosphorylation.

Role of Rac1 in smooth muscle cells

Vincent Sauzeau

The main objective here is to understand how Rac1 controls the contraction of bronchial smooth muscle cells, to define the mechanisms responsible for the activation of Rac1 in asthma, and to develop Rac1 inhibitors.

Pathophysiology of intracranial aneurysms

Gervaise Loirand

Based on our collaboration with Team I (J.-J. Shott) and the identification of rare causal variants, our objective is to understand the pathophysiology of intracranial aneurysms by developing relevant experimental cellular and animal models (cf. *Crosscutting programs* p16).

Relationships between inflammation and bronchial hyperreactivity

Antoine Magnan

This research pays particular attention to the relationship between Rac1/inflammation/contraction in asthma and confirmation of concepts in human pathology.

HIGHLIGHTS

Discovery of the role of leukocyte RhoA exchange factor Arhgef1 in vascular inflammation and atherosclerosis

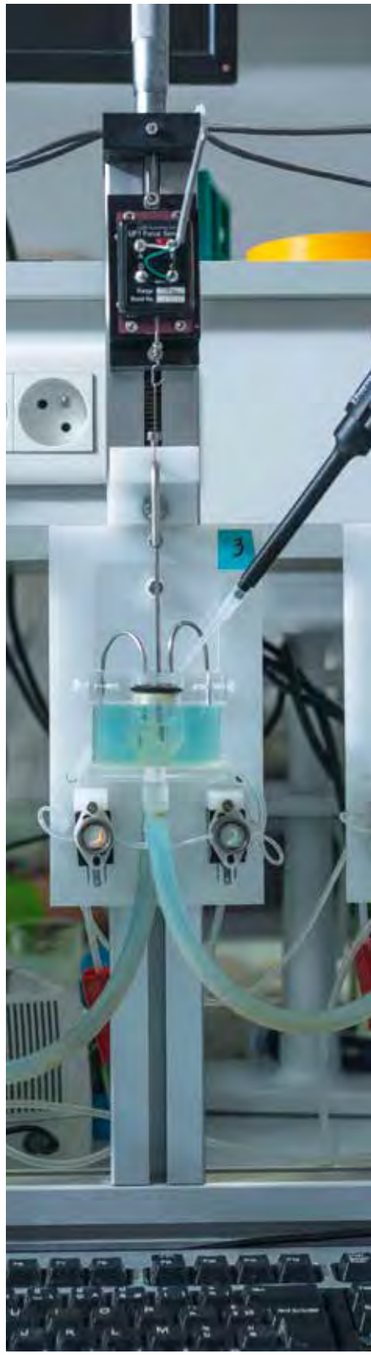
Carbone ML et al., *J Clin Invest*, 2017; 127(12): 4516-4526

We have previously demonstrated that the RhoA exchange factor Arhgef1 plays an essential role in the vasoconstrictor and hypertensive effect of angiotensin II (Ang II) (Guilluy C. et al., *Nat Med* 2010). In this study, we describe the role of Arhgef1 in the pro-inflammatory and pro-atherogenic effects of Ang II. We show that atherosclerosis is very strongly limited in mice that do not express Arhgef1. Bone marrow transplantation in irradiated mice demonstrates that the deletion of Arhgef1 in leukocytes is responsible for this protection against atherosclerosis. We have then identified the molecular mechanisms involved by showing that Arhgef1 is essential for the activation of leukocyte integrins responsible for the adhesion of leukocytes to the endothelium and their penetration into atherosclerosis plaques in mice and humans. This work confirms the identification of Arhgef1 as a therapeutic target of interest to develop innovative therapeutic strategies to reduce cardiovascular risk factors and arterial disease. To move forward towards this objective, we have now set up a collaborative project with medicinal and computational chemists to design, synthesize and test original chemical inhibitors of Arhgef1/RhoA signaling.

Targeting of Rac1 prevents bronchoconstriction and airway hyperresponsiveness

André-Grégoire G et al., *J Allergy Clin Immunol*, 2018; 142(3):824-833

This study demonstrates the involvement of the small G protein Rac1 in bronchial hyperresponsiveness associated with allergic asthma in a murine model and in humans. We show that Rac1 controls intracellular calcium and is necessary for the contraction of airway smooth muscle cells. We identified phospholipase Beta2 as an effector of Rac1. Indeed, the production of inositol 1,4,5-trisphosphate by phospholipase Beta2 and the resulting release of calcium from intracellular stores that trigger contraction, depend on Rac1 activation. Specific deletion of Rac1 in smooth muscle cells or pharmacological inhibition of Rac1 reduces airway hyperresponsiveness in a mouse model of allergic asthma. An over-activation of Rac1 is observed in airways of mouse model of allergic asthma and in patients with asthma. These results identify Rac1 as a therapeutic target for the treatment of asthma, particularly of its severe forms that are resistant to standard treatments. This work has led to the development of new pharmacological inhibitors of Rac1, effective in mouse models of allergic asthma, which has allowed the filing of three patents and the NaRacAS clinical trial (NCT03325088) coordinated by Antoine Magnan.



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DYSLIPIDEMIA AND LIPOTOXICITY

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TEAM IV

DYSLIPIDEMIA AND LIPOTOXICITY

BERTRAND CARIOU

BERTRAND CARIOU
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B. Cariou obtained his MD (University of Nantes) and PhD (University Paris XI) in 2003. He completed his post-doctoral training at the Institut Pasteur, Lille (Pr B. Staels) on the metabolic role of the bile acid receptor FXR. He joined *l'institut du thorax* in 2006 and became Professor of Endocrinology at the Nantes University Hospital in 2009. Since 2015, he has been the elected director of *l'institut du thorax*. He obtained the Apollinaire Bouchardat (2009) and Auguste Loubatières (2017) awards from the French Society of Diabetes. Pr. Cariou is interested in the function of PCSK9 and is a core member of a TransAtlantic Network of Excellence on PCSK9 funded by the Fondation Leducq (2014–2019). He is also the coordinator of RHU project CHOPIN (2016-2021), aiming to identify new targets in LDL-cholesterol metabolism.

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Our team focuses on the identification of new physiological and molecular pathways in **lipoprotein metabolism and cardiovascular diseases**. Among cardiovascular risk factors, LDL-cholesterol (LDL-C) plays a critical role in the development of atherosclerosis. The first goal of our team is therefore to improve deciphering of the hepatic and intestinal metabolism of LDL in order to identify new pathways and ultimately **new drug targets for hypercholesterolemia** (cf. *Crosscutting programs RHU CHOPIN* p.16). We also use seipin knockout mice as a unique model of congenital generalized lipodystrophy to decipher the molecular links between **adipocyte dysfunction and cardiometabolic complications** ◆

RESEARCH PROGRAMS

Identification and characterization of the non-canonical functions of PCSK9, especially in the small intestine, endocrine pancreatic beta cells and in development during the differentiation of human induced pluripotent stem cells.

Cédric Le May, Karim Si-Tayeb

Identification of new causative genes in familial hypobetalipoproteinemia (FHBL) for further deciphering LDL-C metabolism and identifying new drug targets.

Bertrand Cariou

Deciphering the function of seipin in order to identify new molecular pathways involved in mature adipocyte biology.

Xavier Prieur, Jocelyne Magré

To assess these goals, we have built a multi-skilled team with a highly translational approach, highlighted by our contribution in the field of PCSK9, a master regulator of LDL-C homeostasis and a validated drug target for hypercholesterolemia. We are notably working in close interaction with the CIC 'Endocrinology & Nutrition' (CHU NANTES, INSERM 1413; scientific coordinator: Bertrand Cariou; translational project manager: Matthieu Pichelin) to recruit patients and conduct both observational and interventional clinical studies. We have also acquired a well-reputed expertise in the *in vivo* phenotyping of lipoprotein metabolism in mice, with a specific focus on intestinal lipoprotein metabolism. We are notably working on trans-intestinal cholesterol excretion or TICE (Cédric Le May). In parallel we have developed innovative tools to address our scientific questions such as, for instance, urine sample-derived human induced pluripotent stem cells (UhiPSC) differentiated in hepatocytes (Karim Si-Tayeb) or an inducible seipin knock-down adipocyte cell line (Xavier Prieur).

HIGHLIGHTS

A new mouse model to decipher the intestinal function of PCSK9

Le May C & Cariou B, *unpublished results*

Besides the liver, PCSK9 is expressed along the intestinal cephalo-caudal axis in mice and in human enterocytes, as demonstrated in jejunal and ileal biopsies, as well as in the Caco-2 enterocytic cell. We demonstrated that no circulating PCSK9 could be detected in the peripheral blood stream or portal vein of liver-specific PCSK9 knockout mice indicating that PCSK9 may only act in an autocrine/paracrine manner after production by enterocytes. Regarding the potential function of intestinal PCSK9, we previously showed that the increase in postprandial triglyceride levels after an olive oil gavage were less pronounced in PCSK9-knockout (KO) mice. This could be a consequence of either an increased clearance of triglyceride-rich lipoproteins (TRLs) through an enhanced hepatic uptake or an increased intestinal secretion of chylomicrons. The later hypothesis is supported by observations in PCSK9 KO mice and in *in vitro* experiments with Caco-2 cells in which PCSK9 modulated apoB48 secretion (Le May C et al. *Arterioscler Thromb Vasc Biol* 2009; 29: 684-90).
To unravel the potential autonomous role of intestinal PCSK9 in TRL metabolism, we generated a mouse model with specific intestinal PCSK9-deficiency. To obtain intestinal specific KO mice (i-Pcsk9-/-) mice, we have respectively bred the flox/flox mice with transgenic mice expressing CRE under either the villin promoter (Vil-CRE+). As expected, we observed by Q-PCR a severe reduction of PCSK9 mRNA levels in the proximal, medial and distal segments of the small intestine of i-Pcsk9-/- mice without any change in the liver. Consistently, *hybridization in situ* confirmed the disappearance of the PCSK9 labelling in the gut of i-Pcsk9-/- mice compared to control floxed mice.
Importantly, we did not find any effect of the intestinal deletion of PCSK9 on plasma triglyceride, plasma cholesterol or plasma PCSK9 levels on low or a high-fat diet. We next studied the impact of hepatic PCSK9 deficiency *in vivo* on postprandial lipemia. Interestingly, as already seen with full PCSK9 KO mice, liver Pcsk9-/- mice exhibit an altered postprandial response compared with control floxed mice. By contrast, we did not detect any alteration of the postprandial lipemia in the i-Pcsk9-/- mice.
Altogether these data suggest either that the intestinal form of PCSK9 does not exert a major effect on TRL metabolism or that the circulating PCSK9 (from hepatic origin) compensates for the absence of the intestinal intracellular form. In order to address this question, we are now generating some double liver and intestinal Pcsk9-deficient mice (i-Pcsk9-/- injected with AAV8 CRE recombinase).

Seipin KO mice: a unique model of diabetic cardiomyopathy

Joubert M et al. Diabetes 2017; 66: 1030-40

Type 2 diabetes mellitus (T2DM) is a well-recognized independent risk factor for heart failure (HF) that reaches approximately 12% in this population. On the one hand, a large body of work indicates that diabetic cardiomyopathy is associated with altered cardiac energy metabolism. Indeed, in obese T2DM patients, cardiac lipid uptake is increased. On the other hand, the diabetic heart is also characterized by impaired insulin-stimulated glucose uptake and obvious signs of glucose overload: oxidative stress, glycation, and hexosamine biosynthetic pathway (HBP) chronic activation. As most available T2DM animal models simultaneously display dysregulated lipid and carbohydrate metabolism, the exact relative contributions of lipotoxicity and glucotoxicity remain unclear.
In order to provide new insights into the mechanism driving the development of diabetic cardiomyopathy, we have the advantage of our unique model of lipodystrophic seipin knockout (SKO) mice that display a quasi-absence of adipose tissue associated with severe insulin resistance and diabetes (Prieur X et *al. Diabetologia* 2013; 56: 1813-25). Using echocardiography and cardiac magnetic resonance imaging, we showed that SKO mice display cardiomyopathy with left ventricular hypertrophy and diastolic dysfunction. Surprisingly, neither intramyocardial lipid accumulation nor lipotoxic hallmarks were detected in SKO mice. 18F-FDG positron emission tomography showed increased myocardial glucose uptake. Consistently, the O-GlcNAcylated protein levels were markedly increased in the SKO heart, suggesting a glucose overload. We therefore hypothesize that in SKO mice, chronic hyperglycemia activates HBP, inducing elevated O-GlcNAc protein levels, which in turn alters the cardiac function. To test this hypothesis, we treated SKO mice with the oral antidiabetic drug SGLT2 inhibitor (SGLT2i) dapagliflozin that successfully prevented the development of hypertrophic cardiomyopathy.

The SKO mouse model therefore represents a unique opportunity to highlight the exact contribution of chronic HBP activation in the pathophysiology of diabetic cardiomyopathy. Importantly, the cardiovascular outcome trials with SGLT2i decreased the cardiovascular mortality and HF in patients with T2DM. Therefore, our results suggest the hypothesis that the HBP normalization takes part in the beneficial cardiovascular effect of SGLT2i.

A proof of concept study demonstrating the relevance of TICE in Human

Moreau F et al. J Clin Lipidol. 2018 ; pii: S1933-2874(18)30408-2

The small intestine plays a crucial role in dietary and biliary cholesterol absorption, as well as its lymphatic secretion as chylomicrons (lipoprotein exogenous way). Recently, a new metabolic pathway called TICE (Trans-Intestinal Cholesterol Excretion) that plays a central role in cholesterol metabolism has emerged. TICE is an inducible way, complementary to the hepatobiliary pathway, allowing the elimination of the plasma cholesterol directly into the intestine lumen through the enterocytes.
In 2013, we demonstrated with Ussing chambers that human jejunal biopsies actively excrete cholesterol from basolateral to luminal chambers, suggesting that TICE is operative and inducible in human (Le May C et al. *Arterioscler Thromb Vasc Biol.* 2013;33(7):1484-93). However, the clinical evidence of TICE in human remains challenged due to the difficulty to discriminate the hepatobiliary and transintestinal routes *in vivo.*
To provide the first proof of concept that TICE exists *in vivo* in humans, we measured plasma, bile and fecal cholesterol excretion by mass spectrometry after intravenous injection of D7-cholesterol in two patients presenting cholangiocarcinomas. No trace of bile acids was detected in the feces of the two patients, validating the total obstruction of their primary bile duct. Importantly, a significant amount of plasma D7-cholesterol was quantified in the feces of the two patients 48h and 72h after the intravenous injection. In conclusion, our data bring the first direct proof that TICE is an active pathway in humans that could be druggable to reduce cardiovascular diseases.

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PUBLICATIONS

2017

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DIURNAL MITOCHONDRIAL RHYTHMS AND METABOLIC DISEASES

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TEAM V

DIURNAL MITOCHONDRIAL RHYTHMS AND METABOLIC DISEASES

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Our overarching goal is to discover novel therapeutic targets in metabolic diseases using a chronobiological approach ◆

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D. Jacobi is specialized in the metabolic complications of overnutrition. After doctoral studies on physical activity assessment in daily life and its applications in subjects with low physical activity levels (PhD, 2011, University of Tours, FR), he moved to the Harvard School of Public Health in Boston for a postdoctoral fellowship. He studied the circadian regulation of liver metabolism in the Department of genetics and complex diseases (Pr. Chih-Hao Lee). His research area is on the molecular mechanisms of metabolic diseases in the context of obesity with a focus on the alteration of daily metabolic cycles of sub-cellular organelles. David Jacobi is a laureate of an "ATIP-Avenir 2016 grant": a joint CNRS/ Inserm French grant aiming at attracting young high-level researchers to lead research teams on new research topics. He joined *l'institut du thorax* to develop a new research team.

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RESEARCH PROGRAMS

Overweight and Non-Alcoholic Fatty Liver Disease (NAFLD) affect 50% and 25% of European adults, respectively. NAFLD predicts type 2 diabetes, cardiovascular diseases, steato-hepatitis, and hepatocellular carcinoma but has limited therapeutic options. Initially postulated to be "a tale of two-hits" with fat deposition followed by inflammation, NAFLD in fact implicates multiple signaling pathways. These pathways are influenced by the molecular circadian clock, an evolutionary conserved endogenous mechanism that anticipates daily environmental changes by generating behavioral and biological 24-h rhythms. In mammals, a hypothalamic pacemaker adjusts basic physiological functions to the night/day cycles, but peripheral organs also possess an intrinsic circadian clock. The liver clock, for instance, fine-tunes metabolism by supporting metabolic flexibility, the capacity to adapt fuel oxidation to fuel availability. In fact, abnormal feeding schedules impose a circadian misalignment contributing to metabolic disorders, but the molecular links remain elusive and constitute an intense area of research.

To this end, D. Jacobi has provided the first evidence that the circadian clock and feeding rhythms orchestrate mitochondrial dynamics to adjust metabolism across daily cycles of energy intake. Mitochondrial dynamics modulate mitochondrial network and quality control mechanisms: a fused network enhances bioenergetic efficiency whereas fission limits the oxidative stress during nutrient overload. Importantly, loss of this process through genetic disruption of the hepatic circadian triggers fatty liver disease. By bringing together the circadian and mitochondrial research fields, we aim to unravel the natural history of mitochondrial dysfunction. This will provide a new paradigm whereby disrupted mitochondrial rhythms are pivotal in hepatic metabolic disease. It can open the way for innovative chronopharmacology and provide a physiological rational for chrononutrition.

The future of chronobiology research relies on translation to clinical medicine. The team project is a fundamental part of this endeavour, as it will provide the preclinical proof of concept for moving scientific knowledge to clinical research on metabolic diseases. We use genetic, pharmacological, and metabolic approaches to decipher the molecular mechanisms by which overnutrition and circadian dyssynchrony disturbs mitochondrial rhythms. We then work to establish how these alterations trigger metabolic diseases. The team benefits from the unique environment of *l'institut du thorax* and its research unit to demonstrate the relevance of its findings in clinical populations of patients with obesity.

HIGHLIGHTS

Since the team's creation in January 2017, we focused our efforts on structuring the team and setting up the necessary equipment to manage the project, recruiting the team, initiating effective collaborations, and securing additional funding.
David Jacobi recruited a PhD student (Manon Durand) and a postdoctoral researcher (Florian Atger, PhD 2016, Nestlé Institute of Health Science and University of Lausanne, Switzerland) to work on circadian profiling of mitochondria in mouse liver. Since its arrival in Nantes, F. Atger has since secured extra funding from the Société Francophone du Diabète (Allocation Jeune Chercheur Francophone 2018).

The team developed its capacities for circadian studies. It set-up a dedicated space in the animal facility for mouse phase entrainment to defined light-dark cycles and acquired two computer-programmable ventilated boxes (two A-Box 160 PP, Noroit, France).
Since management of oxidative stress is central in our working hypotheses, the team acquired an electronic paramagnetic resonance (EPR) spectrometer for oxidative/nitrosive stress measurement (MiniScope MS 5000, Magnettech, Germany) and is using complementary techniques (HPLC, LC-MS, redox blotting, and EPR) to identify specific ROS generated in cells and tissues. The use of the EPR techniques can be extended to human tissues.

Daniel Mauvoisin (PhD 2011, Université du Québec à Montréal, Canada) will join the team as a senior post-doctoral researcher in 2019. Daniel Mauvoisin post-doctoral studies (University of Lausanne, Circadian rhythms lab and Nestlé Institute of Health Science, Diabetes and Circadian rhythms department, Switzerland) directed by Frédéric Gachon, extended the knowledge of rhythmic orchestration of the hepatic proteome. They also stressed the importance of post-translational modifications such as phosphorylation and acetylation in the regulation of the proteome and also clarified the respective roles of the circadian clock and signals regulated by the dietary rhythm. Upon its arrival, Daniel Mauvoisin will develop a new project funded by the "Excellence and attractiveness in research" of the NExT (Nantes Excellence Trajectory) initiative. NExT is a laureate of the I-SITE call for projects of the programme d'investissement avenir 2 (PIA2) (cf. *NExT* p.17). He will develop at *l'institut du thorax* a research program to understand how the circadian clock controls cellular metabolism and mitochondrial function and ultimately, to apply this knowledge to the treatment of metabolic diseases in humans. He will focus on NAFLD with a chronobiological approach and propounds that specific post-translational modifications of proteins could represent a novel pathophysiological mechanism.

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PUBLICATIONS

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EMERGING TEAM

MEDICAL GENETICS

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S. Bézieau is Head of medical genetics department at CHU of Nantes. After his pharmaceutical studies (PharmD, 1996), he became interested in biology, specializing in molecular genetics (PhD in Molecular Genetics, 2000). He continued his research in the field of oncogenetics between 2000 and 2010 and participated in the GECCO (Genetics and Epidemiology of Colorectal Cancer) consortium. Since 2013, he has focused on the discovery of new genes involved in intellectual disabilities (PHRC HUGODIMS); this topic has been investigated through major international collaborations with renowned partners such as the Baylor College of Medicine and Duke University. In February 2018, he was elected President of the French Federation of Human Genetics. He is also an elected member of the Board of Directors of the French Foundation for Rare Diseases.

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Our team, which joined *l'institut du thorax* in February 2018, includes the members of the department of medical genetics of Nantes University Hospital, one of the largest of its kind in France. Our objective is to further strengthen our existing collaborations in cardiovascular research with the other members of the laboratory, and to facilitate translational research in cardiovascular genetics by transferring any medically relevant genetic discovery to molecular diagnostics ◆

RESEARCH PROGRAMS

Genetics of intellectual disability
Stéphane Bézieau

Molecular bases of inherited erythrocytosis
Betty Gardie

In each program, patient recruitment is ensured in the context of molecular diagnostics. Since 2010, we have identified a dozen new genes responsible for intellectual disability (ID) through our high-throughput sequencing approaches and international collaborations, notably including the Baylor College of Medicine (Houston, Texas). In parallel, we have recently reported a new molecular mechanism causing erythrocytosis through the involvement of a cryptic exon in the *VHL* gene. Gene discovery is a starting point only though: functional investigations are needed to further understand the molecular mechanisms underlying disease. To advance on these issues, our strategy is based on molecular approaches applied to stem cells derived from the patients. In complement, we have developed tight collaboration with the Zebrafish Modeling Center at Duke University, enabling us to model the consequences of gene mutations involved in syndromic ID.

HIGHLIGHTS

Identification and understanding of genes causing rare diseases
Küry S et al. *Am J Hum Genet* 2017 Feb 2; 100(2): 352-363
Guissart C et al. *Am J Hum Genet* 2018 102(5): 744-759

Our team has made a very significant contribution to the identification of new genes responsible for rare diseases, particularly ID, in recent years. These discoveries were made possible through the recruitment of patients by consultations at the medical genetics department and the high level of expertise in high-throughput genomic analysis. The starting point was the coordination of a Hospital Clinical Research Project (PHRC) called HUGODIMS (Interregional Project of the Great West of France for the Exploration by Exome Approach of Molecular Causes of Moderate or Severe Intellectual Disability. Seventy-six patients with moderate to severe isolated or syndromic ID were included, in six hospitals, during genetic consultations performed over a 6-month period in 2014. These patients had been selected on clinical criteria and obviously after exclusion of Fragile X syndrome, or abnormalities observed by karyotype, or by Comparative genomic hybridization. The strategy implemented was the sequencing of exome trios (parental DNA was also sequenced) in order to facilitate the interpretation of data for the identification of new genes, thanks to the expected *de novo* status of a large number of mutations. This PHRC yielded a 40% diagnostic rate within the cohort, which is much higher than the 14% rate of molecular abnormalities found by sequencing the 44 main genes known in ID. At the research level, this work allowed the identification of new candidate genes in 20% of the ID cases. In addition, this work has prompted very successful international collaborations, notably with Baylor College of Medicine, to assemble cohorts of patients with the same rare disease caused by mutations in the same gene. Likewise, a collaboration with the Zebrafish modeling laboratory (Duke University) provided insight into the pathogenicity of the variants by showing their impact in mutant fishes. This collaborative strategy led to about 20 high-level international publications (2016–2018), while several others are currently being reviewed (e.g., a manuscript by Cogné et al. reviewed favorably by the American Journal of Human Genetics) (or in preparation Latypova et al.). Given the results obtained in the first HUGODIMS series, additional funds were allocated to our team for the sequencing of 80 additional trios. The HUGODIMS 2 project is currently in progress. At the same time, the Fondation Maladies Rares [French Foundation for Rare Diseases] has funded sequencing by the genome-trios approach for about twenty patients whose cause of disorder could not be explained by exome trio analysis. The first data (unpublished) have yielded promising results, with the identification of four molecular causes out of seven trios analyzed to date.

Identification of a new VHL exon and complex splicing alterations in familial erythrocytosis or von Hippel-Lindau disease
Lenglet M et al. *Blood* 2018 Aug 2; 132(5): 469-483

Since 2015, we have recruited 250 cases with hereditary erythrocytosis through the department of medical genetics led by Stéphane Bézieau. Next generation sequencing was performed on 187 patients to screen for the presence of mutations in 28 genes. We identified 47 variants (25% patients) in 12 genes and set up functional studies of seven genes. Notably, we identified a complex regulation of *VHL* splicing. We first demonstrated that synonymous mutations may induce exon skipping. More importantly, we identified a new *VHL* cryptic-exon (which we termed E1'), deep in intron 1, which was mutated in patients with erythrocytosis or *VHL* disease. A comprehensive study was performed on mutations in E1' (microsatellite analysis, segregation studies, phylogenetic analysis, expression measurement of mRNA and proteins, functional studies of the potential VHL1' protein, minigene experiments and RNA sequencing of biological samples from the patients). We showed that the mutations induce a dysregulation of *VHL* splicing with excessive retention of E1'. In both cases (exon skipping or retention), splicing dysregulation differentially impacts splicing in correlation with phenotype severity and is associated with a downregulation of VHL protein expression. In parallel, we set up a cellular model of hereditary erythrocytosis by starting a collection of hiPS from patients. We differentiated the hiPS in erythropoietin-producing cells (responsible for erythrocytosis) of the liver type that produces EPO during fetal life (in collaboration with K. Si-Tayeb, team IV), and for the first time in neural crest cells, the cell type responsible for EPO production in adults (paper in preparation).

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CORE FACILITIES

CORE FACILITY

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GenoBiRD offers full services for high-throughput sequencing (genomes, exomes, gene capture, etc.), genotyping and genome expression projects (RNA-Seq, 3'seq RNA profiling and microarrays), from wet lab to data analysis. GenoBiRD also provides open access to wet-lab equipment and IT resources for bioinformatics.

This core facility is a cornerstone for sharing infrastructures, software, datasets, and biomedical data analytics expertise, aiming to develop novel integrative approaches combining clinical and multi-omics data.

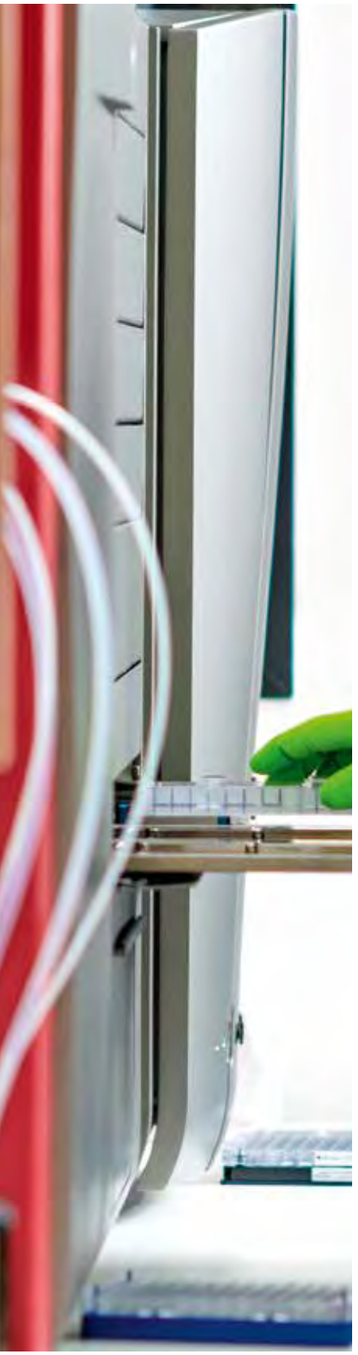
GenoBiRD gathers two core facilities (Genomics and Bioinformatics) run by dedicated and highly qualified staff.

GenoBiRD is recognised as a national infrastructure by the IBiSA organisation, and is member of the Biogenouest network, through which it receives regular support from the Pays-de-la-Loire regional council ◆

EXPERTISE

- **High-throughput sequencing (NGS): whole genomes or exomes, capture of targeted genes**
- **High-throughput genotyping (Axiom array plates)**
- **Transcriptome study (RNA-seq, 3'seq RNA profiling, microarrays)**

We provide services such as automated library preparation and sequencing, and imputation across genotyping arrays.
For all of these applications, the Bioinformatics core facility BiRD can provide expertise in large-scale data analysis and dedicated pipelines to standardize analyses from raw data to biological significance (Snakemake and Galaxy workflows). BiRD also offers training sessions on data analysis and programming languages.



SERVICES

- **Project management:** for every project we meet the principal investigator in order to discuss the content of the study including design, methods, dates and time limits, and analysis.
- **Open access:**
  - — **Wet-lab equipment:** access includes training and support by the core facility staff
  - — **Bioinformatics resources:** computer cluster nodes and storage, Galaxy portal

EQUIPMENT

- **Two high-throughput sequencers** (Illumina HiSeq and MiSeq)
- **Genotyping station and expression profiling** (Affymetrix GeneTitan ™)
- **A microarray scanner** (InnoScan)
- **Real-time PCR device** (Roche LC480)
- **Small wet lab equipment**
- **Computing (1,600 cores) and storage (800 TB) infrastructure,** directly connected to the sequencers and allowing remote access (Clusters, OpenStack Cloud) to all researchers regardless of their host institution.

MAIN PARTNERS (PUBLIC / PRIVATE)

GenoBiRD hosts around thirty projects a year. The core facility is partner of the following projects:

- **Fondation Maladies Rares:** partnership in DNA sequencing services
- **VaCaRMe:** regional program in research, training and innovation focusing on risk assessment of aging-related chronic diseases, particularly related to the cardiovascular, metabolic and respiratory systems (Scientific Direction: Richard Redon)
- **ERRATA:** Study of the Relation between resistance to treatment and apoptosis in Anticancer Therapies (Scientific Coordinator: François Vallette, CRCINA)
- **GRIOTE (Research Group in Omics Data Integration at Very Large Scale):** collaborative bioinformatics project in Pays de la Loire region.
- **SYMETRIC (Systems Medicine: Toward a Research & Innovation Center):** Regional Federation Project in Systems Medicine
- BiRD operates a cloud infrastructure and contributes to a harmonization effort on national computing, through the **Biosphere federation initiative by the IFB (Institut Français de Bioinformatique).**
- **SysMics (Toward Systems Medicine based on Genomics)** SysMics aims to federate the NExT scientific community toward a common objective: foresee the emergence of systems medicine by co-developing three approaches in population-scale genomics: genotyping by sequencing, cell-by-cell profiling and microbiome analysis.

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CORE FACILITY

THERASSAY

FLAVIEN CHARPENTIER

THERASSAY is a core facility of functional exploration in small animals, which supplies a large range of technological equipment and scientific expertise to academic and industrial research groups.

This open core facility offers a unique service, from the generation of animal models to highly specialized functional analyses of cardiovascular, metabolic, respiratory, digestive and motor functions as well as tumorigenesis exploration. THERASSAY involves multi-disciplinary teams from several laboratories of Nantes (*l'institut du thorax*, INSERM UMR 1087/CNRS UMR 6291, INSERM UMR 1235, INSERM UMR 1232, INSERM UMR 1089).

THERASSAY is labeled by the national network of IBiSA facilities and integrated in Biogenouest (Western France life science and environment core facility network). THERASSAY receives support from the Pays-de-la-Loire regional council.

THERASSAY accepts to perform projects as services or collaborations.

THERASSAY also offers access to its equipment and trains students, technicians and researchers in the use of this equipment.

THERASSAY has been certified ISO: 9001 v2015 since January 2017 ◆

Lead Scientist
Flavien CHARPENTIER, PhD

Team
Maud CHETIVEAUX, PhD
Virginie AILLERIE
Grégory BOUCHAUD, PhD
Marie-Aude CHEMINANT
Agnès HIVONNAIT
Benjamin LAUZIER, PhD
Cédric LE MAY, PhD
Gervaise LOIRAND, PhD
Antoine MAGNAN, MD, PhD
Marc RIO

CONTACT

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SERVICES

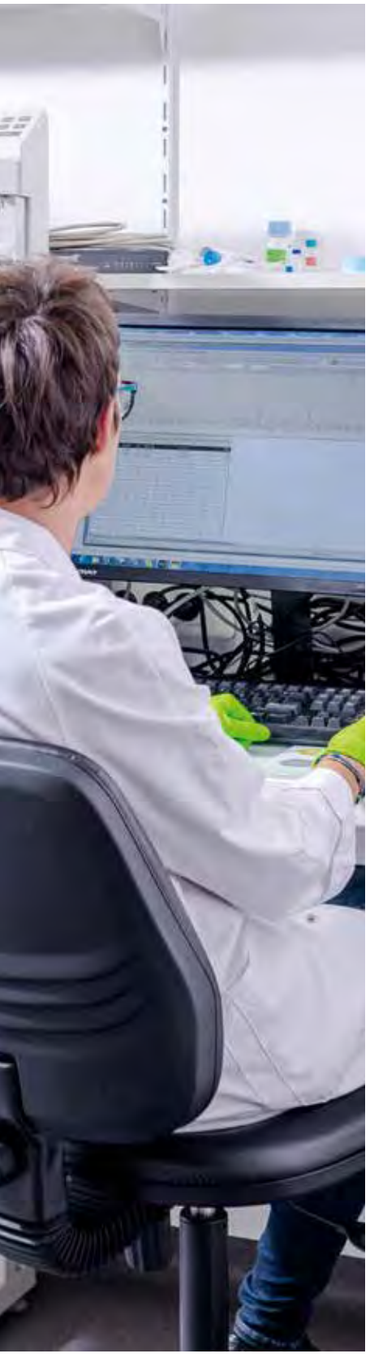
THERASSAY services are structured into 7 modules:

1. Generation of animal models of human pathologies

(diabetes, dyslipidemia, hypertension, asthma, heart failure, cardiomyopathy, etc.)

2. Metabolic function

- **Glucose homeostasis and insulin-related pathways:** glycaemia, insulinemia, glucose tolerance test and insulin sensitivity
- **Lipid homeostasis:** lipoprotein profile, biomarker quantification (HDL-C, LDL-C, cholesterol, NEFA, TG, Glycerol, CETP activity, adiponectin, biliary acids, etc.)
- **Metabolic cages:** energy expenditure, food and drink consumption, urine and feces collection
- **Animal models:** models of dyslipidemia (cholesterol and fructose diet, LDLr-/-, ApoE-/-), obesity (ob/ob mice), diabetes (db/db mice, streptozotocin model) and hypoglycemic seizures.



3. Vascular function

- ***In vivo*:** systemic and pulmonary arterial pressure, acute vasoreactivity
- ***Ex vivo*:** contractility assays (intact and permeabilized arteries), arteriography
- ***In vitro*:** migration, proliferation, apoptosis on vascular cell models
- **Animal models:** arterial hypertension (L-NAME, Angiotensin II), pulmonary arterial hypertension (hypoxic chamber)

4. Cardiac function

- **Cardiac electrophysiology:** ECG, catheter-mediated intracardiac recording, multi-electrode arrays, action potential recording with sharp microelectrodes, high-throughput fluorimetry, patch-clamp
- **Cardiac contraction:** echocardiography-Doppler, pressure-volume loops, isolated working heart, contractility assays on isolated cardiomyocytes and papillary muscles.
- **Animal models:** septic shock, ischemic heart failure, progressive cardiac conduction disease, dilated cardiomyopathy, type 3 long QT syndrome

5. Respiratory function

- ***In vivo*:** airway resistance and hyperresponsiveness (plethysmography and flexivent©), pharmacological assays of molecules delivered in situ by aerosol via bronchial tubes
- ***In vitro*:** flow cytometry analysis of cells from broncho-alveolar lavage, lung, spleen and lymph nodes, analysis of immune serum globulins, morphological modification analysis on histological lung slides
- **Animal models:** acute and chronic asthma models (ovalbumin and house dust mite extract)

6. Motor and cognitive function

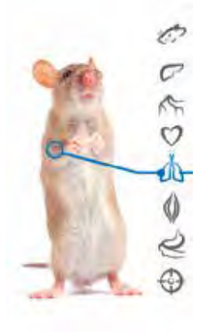
- ***In vivo*:** force, locomotion, training, coordination, gait endurance (motor) and stress, anxiety, curiosity, and spatial, olfactory memory (cognition)
- ***Ex vivo:*** muscular force measurements, contractile properties and calcium homeostasis
- **Animal models:** Duchenne muscular dystrophy, muscular atrophy, and sarcopenia

7. Digestive function

- ***In vivo:*** transit, gastric emptying, intestinal permeability and confocal endomicroscopy
- ***Ex vivo:*** gastrointestinal motility (organ bath) and paracellular permeability (Ussing chamber)
- **Animal models:** disorders of digestive motility, intestinal inflammatory diseases (TNBS, IL10-/-), neurodegenerative diseases (e.g., rotenone)

8. Onco-hematology

- **Human myeloma** cell line testing and evaluation
- ***In vitro:*** cell survival, proliferation, apoptosis, and cellular mechanisms using various *in vitro* assays
- ***In vivo:*** injection of human myeloma cells into immunodeficient mice, behavioral and tumor volume monitoring



Metabolic

Vascular

Cardiac

Respiratory

Neuro-motor

Digestive

Onco-hematology

EQUIPMENT

THERASSAY possesses specific equipment for each explored function, including:

- FPLC and HPLC for lipoprotein profiles
- Metabolic chambers
- Telemetry, Tail-Cuff, Arteriograph
- Echocardiograph, ECG, Intracardiac electrophysiological recording setup, Pressure-volume loops, Isolated working heart, patch clamp, CellOptic© (fluorimetry-based action potential recording), multi-electrode arrays (MEA)
- Plethysmograph, Flexivent©
- Actimeter, Grip Test, Rotarod, Wire test, Wire Hang, Treadmill, Gait analysis, Open field 3D, Elevated plus Maze
- Ussing chamber, confocal endomicroscope
- Isolated-organ bath
- Luminex©, Hematology
- Cell culture, Microscopy, Histology

PUBLICATIONS

2017

Caudal D, Guinobert I, Lafoux A, Bardot V, Cotte C, Ripoche I, Chalard P, Huchet C.
Skeletal muscle relaxant effect of a standardized extract of Valeriana officinalis L. after acute administration in mice. *J Tradit Complement Med.* 2017;8(2):335-340. *(Therassay members as co-authors)*

Carbone ML, Chadeuf G, Heurtebise-Chrétien S, Prieur X, Quillard T, Goueffic Y, Vaillant N, Rio M, Castan L, Durand M, Baron-Menguy C, Aureille J, Desfrançois J, Tesse A, Torres RM, Loirand G.
Leukocyte RhoA exchange factor Arhgef1 mediates vascular inflammation and atherosclerosis. *J Clin Invest.* 2017;27(12):4516-4526. *(Therassay acknowledged)*

André-Grégoire G, Dilasser F, Chesné J, Braza F, Magnan A, Loirand G, Sauzeau V.
Targeting of Rac1 prevents bronchoconstriction and airway hyperresponsiveness. *J Allergy Clin Immunol.* 2017; 42(3):824-833. *(Therassay acknowledged)*

Derangeon M, Montnach J, Cerpa CO, Jagu B, Patin J, Toumaniantz G, Girardeau A, Huang CLH, Colledge WH, Grace AA, Baró I, Charpentier F.
Transforming growth factor β receptor inhibition prevents ventricular fibrosis in a mouse model of progressive cardiac conduction disease. *Cardiovasc Res.* 2017;113(5):464-474. *(Therassay acknowledged)*

Harford-Wright E, Andre-Gregoire G, Jacobs KA, Treps L, Le Gonidec S, Leclair HM, Gonzalez-Diest S, Roux Q, Guillonneau F, Loussouarn D, Oliver L, Vallette FM, Foufelle F, Valet P, Davenport AP, Glen RC, Bidere N, Gavard J.
Pharmacological targeting of apelin impairs glioblastoma growth. *Brain.* 2017;140(11):2939-2954. *(Therassay acknowledged)*

2018

Regnault C, Usal M, Veyrenc S, Couturier K, Batandier C, Bulteau AL, Lejon D, Sapin A, Combourieu B, Chetiveaux M, Le May C, Lafond T, Raveton M, Reynaud S.
Unexpected metabolic disorders induced by endocrine disruptors in Xenopus tropicalis provide new lead for understanding amphibian decline. *Proc Natl Acad Sci USA.* 2018;115(19):E4416-E4425. *(Therassay members as co-authors)*

André-Grégoire G, Dilasser F, Chesné J, Braza F, Magnan A, Loirand G, Sauzeau V.
Targeting of Rac1 prevents bronchoconstriction and airway hyperresponsiveness. *J Allergy Clin Immunol.* 2018 Sep;142(3):824-833. *(Therassay acknowledged)*

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Food allergen-sensitized CCR9+ lymphocytes enhance airways allergic inflammation in mice. *Allergy.* 2018 Jul;73(7):1505-1514. *(Therassay acknowledged)*

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Piperidinyl-embeded chalcones possessing anti PI3Kδ inhibitory properties exhibit anti-atopic properties in preclinical models. *Eur J Med Chem.* 2018 Oct 5;158:405-413. *(Therassay acknowledged)*

TRAINING

STUDENTS 2017 – 2018

L'institut du thorax is one of the few structures that combines innovative approaches in epidemiology, genomics, bioinformatics, cell & molecular biology, integrated physiology and clinical research on a single site, making it an ideal training ground for Bachelor, Master and PhD students. Each year, we welcome on average 25 master students (MSc), and 9 students obtain their doctorate degree (PhD) ◆

MASTER STUDENTS

MASTER 2 "BIOLOGY, BIOTECHNOLOGY AND THERAPEUTIC RESEARCH", UNIVERSITY OF NANTES

Yasemin Altuntas (Team IIa – Charpentier)
Lucie Audineau (Team IV – Cariou)
Alexia Blandin (Team IV – Cariou)
Valentin Bon-Baret (Team IIb – De Waard)
Robin Canac (Team IIa – Charpentier)
Manon Chiffolleau (Team V – Jacobi)
Olfa Chkir (Team IIb – De Waard)
Bastien Cimarosti (Team IIa – Charpentier)
Yoann Combot (Team IV – Cariou)
Constance Delwarde (Team I – Schott)
Manon Denis (Team IIb – De Waard)
Justine Dhot (Team IIb – De Waard)
Eléonore Dijoux (Team V – Jacobi)
Thomas Dupas (Team IIb – De Waard)
Milène Fresneau (Team III – Loirand)
Dominique Harkous (Team IIa – Charpentier)
Benjamin Le Vely (Team III – Loirand)
Rodolphe Ledieu (Team IV – Cariou)
Corentin Louis (Team I – Schott)
Antoine Moui (Team III – Loirand)
Antoine Persello (Team IIb – De Waard)
Fouzia Souab (Team IIb – De Waard)
Lucas Verdure (Team IV – Cariou)

MASTER 2 "GENETICS, GENOMICS AND SYSTEMS BIOLOGY", UNIVERSITY OF NANTES

Leila Benesteau (Team I – Schott)
Pierre Alexandre Cantat (Team IV – Cariou)
Matthieu Charles (GenoBiRD)
Wallid Deb (Emerging Team – Bézieau)
Adeline Goudal (Team I – Schott)

MASTER 2 "BIOINFORMATICS", UNIVERSITY OF NANTES

Charlotte Berthelier (Team I – Schott)
Pauline Moussard (Emerging Team – Bézieau)

MASTER 2 "BIO-CŒUR", PARIS DIDEROT UNIVERSITY

Soraya Anys (Team I – Schott)
Marine Arnaud (Team IIa – Charpentier)
Pauline Etienne (Team IIa – Charpentier)
Clémence Le Seven (Team I – Schott)
David Stevant (Team IIb – De Waard)

MASTER 2 "CELL BIOLOGY, PHYSIOLOGY, PATHOLOGIES", PARIS DIDEROT UNIVERSITY

Antoine Beurnier (Team III – Loirand)
Charly Cortinovis (Team IIb – De Waard)
Damien Minois (Team IIa – Charpentier)

OTHERS MASTERS

Léa Bellenger
M2 Bioinformatique et génomique
Univ Aix-Marseille (Team I – Schott)

Sandro Benichi
M2 Génétique Univ Paris 5 Descartes (Team I – Schott)

Céline Bourdon
M2 Génétique, Génomique Et Biotech
Univ Brest (Team I – Schott)

Sara Butto
M2 Univ Udine, Italie (Team V – Jacobi)

Pierre-Marie Chevillard
M2 Physiopathologies - Univ Tours (Team IIa – Charpentier)

Laurabelle Gautier
M2 UTC Compiègne (Team I – Schott)

Maxime Gérard
M2 Sciences Chirurgicales Paris Sud Univ Paris Saclay (Team IV – Cariou)

Guillaume Guimbretière
M2 Sciences Chirurgicales Paris Sud Univ Paris Saclay (Team I – Schott)

Vincent L'Allinec
M2 Neurosciences UPMC Paris (Team III – Loirand)

Néna Martin
EPHE Paris (Emerging Team - Bézieau)

Marie Wauters
M2 Anvers, Belgique - Erasmus (Team III – Loirand)

PhD STUDENTS

ONGOING PHD THESES

Emeline Amosse (Team I – Schott)
Anne-Sophie Boureau (Team I – Schott)
Robin Canac (Team IIa – Charpentier)
Marco Castagna (Team I – Schott)
Claire Castro (Team IIa – Charpentier)
Marine Charrier (Team IIa – Charpentier)
Bastien Cimarosti (Team IIa – Charpentier)
Benjamin Cogné (Emerging Team – Bezieau)
Luc Colas (Team III –Loirand)
Yoann Combot (Team IV – Cariou)
Stéphan De Waard (Team IIa – Charpentier)
Safa Dehmani (Team III – Loirand)
Justine Dhot (Team IIb – De Waard)
Eléonore Dijoux (Team III – Loirand)
Manon Durand (Team V – Jacobi)
Damien Garçon (Team IV – Cariou)
Joanna Giemza (Team I – Schott)
Clément Guiraud (Team I – Schott)
Martin Klein (Team III – Loirand)
Vincent L'Allinec (Team III – Loirand)
Marion Lenglet (Emerging Team – Bezieau)
Maxime Lorenzini (Team IIa – Charpentier)
Antoine Persello (Team IIb – De Waard)
Alice Rannou (Team IIa – Charpentier)
Méryl Roudaut (Team IV – Cariou)
Lindzy Tossé (Team I – Schott)
Camille Trouillet (Team III – Loirand)

PhD THESES DEFENDED

2017

SAWSAN AL KHOURY
TEAM IIB – DE WAARD
Les venins animaux comme outils de recherche et d'identification de nouveaux composés thérapeutiques.

NEJMA BELAADI
TEAM III – LOIRAND
Régulation de la mitose par la rigidité de la matrice extracellulaire : étude du rôle de la protéine SUN2.

NADJET BELBACHIR
TEAM IIA – CHARPENTIER
Caractérisation phénotypique d'un nouveau gène impliqué dans le syndrome de Brugada : Le gène *RRAD*.

ROMAIN BOURCIER
TEAM I – SCHOTT
Étude génétique des anévrismes intracrâniens.

MARINE CARRERE
TEAM IIA – CHARPENTIER
Histoire de l'interface entre recherche biologique et médecine en France depuis 1960.

LAURE CASTAN
TEAM III – LOIRAND
De l'allergie alimentaire à l'asthme : rôle de CCR9.

MARINE FERRON
TEAM IIB – DE WAARD
Identification de nouvelles cibles thérapeutiques dans l'insuffisance cardiaque à fraction d'éjection préservée et le choc septique.

OLFAT MALAK
TEAM IIA – CHARPENTIER
Interactions moléculaires dans les canaux dépendants du potentiel. Implications thérapeutiques pour les canalopathies cardiaques et musculaires.

FRANÇOIS MOREAU
TEAM IV – CARIOU
Fonction de l'intestin dans le métabolisme du cholestérol : Rôle de PCSK9 et conséquences des chirurgies bariatriques.

CLÉMENT NIEL
TEAM I – SCHOTT
Développement de stratégies avancées pour l'étude de l'épistasie dans les études d'association génotype-phénotype.

ELODIE PERSYN
TEAM I – SCHOTT
Analyse d'association de variants génétiques rares pour une population démographiquement stable.

VALENTINE PRAT
TEAM IIB – DE WAARD
Identification de nouvelles cibles thérapeutiques pour l'insuffisance cardiaque à fraction d'éjection préservée.

2018

FRANCK CHIZELLE
TEAM IIA – CHARPENTIER
Études fonctionnelles de mutations associées à des pathologies de la repolarisation ventriculaire.

FLORIAN DILASSER
TEAM III – LOIRAND
Rôle in-vivo de la protéine G monomérique Rac1 dans les cellules musculaires lisses de la sphère pulmonaire : implications en physiopathologies bronchiques et vasculaires.

ANDRÉA FONTENEAU
TEAM IIA – CHARPENTIER
Le canal sodique voltage-dépendant $Na_v1.5$: expressions pulmonaires et rôles potentiels dans la fonction respiratoire chez la souris.

XENIA LATYPOVA
EMERGING TEAM – BEZIEAU
Utilisation du modèle poisson zèbre pour l'interprétation de variants dans la déficience intellectuelle d'origine génétique.

JUSTINE PATIN
TEAM IIA – CHARPENTIER
Rôle de Nav1.5, du TGF-beta et de la Cx43 dans les troubles progressifs de la conduction cardiaque.

ZEINA REDA AL SAYED
TEAM IIA – CHARPENTIER
L'étude de maladies du rythme cardiaque en utilisant des cardiomyocytes dérivés des cellules pluripotentes induites.

PhD STUDENT AWARDS

2017

PRIZE FOR THE BEST ORAL COMMUNICATION. DHU 2020 AUTOMN SCHOOL, NANTES, FR
CLAIRE CASTRO

TRAVEL AWARD OF THE INTERNATIONAL GAP JUNCTION CONFERENCE 2017, GLASGOW, UK
JUSTINE PATIN

TRAVEL AWARD OF THE EUROPEAN WORKING GROUP ON CARDIAC CELLULAR ELECTROPHYSIOLOGY, 41THEWGCCE MEETING, VIENNA, AT
ZEINA REDA AL SAYED

POSTER PRIZES. PRINTEMPS DE LA CARDIOLOGIE, NANTES, FR
CLAIRE CASTRO, ANDRÉ **FONTENEAU & JUSTINE PATIN**

2018

CHRISTIAN NEZELOF AWARD - IMAGINE 2018
MARION LENGLET

RESEARCH PRIZE IN PEDIATRIC PATHOLOGY
MARION LENGLET
"Identification of new alteration mechanisms of the VHL (von Hippel-Lindau) gene responsible for VHL or polyglobulia disease".

BETSALEL AUERBACH AWARD – FONDATION DU JUDAÏSME FRANÇAIS
LAURE CASTAN
"Asthma: the role of CCR9".

TRAVEL AWARD OF THE EUROPEAN WORKING GROUP ON CARDIAC CELLULAR ELECTROPHYSIOLOGY, 42NDEWGCCE MEETING, ESSEN, DE
FRANCK CHIZELLE

FIRST PRIZE POSTER CONGRESS OF YOUNG RESEARCHERS OF THE ADELIH, PARIS, FR
MARION LENGLET

POSTER PRIZES, PRINTEMPS DE LA CARDIOLOGIE, MONTPELLIER, FR
FLORIAN DILASSER & VINCENT L'ALLINEC

SEMINARS

The seminars of l'*institut du thorax* are highlights of the scientific experience in our laboratory. They take place every Friday in our research building, the IRS-UN ◆

INTERNAL SEMINARS

Researchers and students are invited to present their work during internal seminars. These seminars are opportunities to share/exchange/discuss with the members of the unit about the progress of our research programs. The objective is to encourage collaboration and scientific communication between teams.

EXTERNAL SEMINARS

Renowned scientists are regularly invited to present their research work (20 to 25 conferences per year). These seminars broaden the scope of expertise of the unit members and open up opportunities for collaboration.

EXTERNAL SEMINARS 2017

CHRISTOPHE BEAULOYE
UNIVERSITÉ CATHOLIQUE DE LOUVAIN, BELGIUM
Transport du glucose et toxicité dans le cœur.

JEAN-PHILIPPE COMBIER
UMR 5546 CNRS-UPS,CASTANET TOLOSAN, FRANCE
Primary transcripts of microRNAs encode regulatory peptides.

FRANCIS COUTURAUD
CHU BREST, FRANCE
Maladie veineuse thromboembolique : de la découverte des thrombophilies biologiques au concept de thrombophilie clinique. Impact sur la prise en charge des patients et des membres de leur famille.

HELENE ELTCHANINOFF & VINCENT RICHARD
CHU DE ROUEN, FRANCE
Innovations rouennaises autour du rétrécissement aortique.

IULIANA IONITA-LAZA
COLUMBIA UNIVERSITY, NEW YORK, USA
A latent Dirichlet allocation model for predicting tissue-specific functional effects of noncoding variation, and applications to complex traits.

TARIK ISSAD
INSTITUT COCHIN, INSERM U1016, CNRS UMR8104, UNIVERSITÉ PARIS DESCARTES, FRANCE
La O-GlcNAcylation des protéines: une modification post-traductionnelle impliquée dans la régulation de la signalisation cellulaire et les processus physiopathologiques.

RONALD KAHN
JOSLIN DIABETES CENTER, HARVARD MEDICAL SCHOOL, BOSTON, USA
Regulation of Adipose Tissue Turnover and Its Communication with Other Tissues.

DANIEL MAUVOISIN
EPFL, LAUSANNE SWITZERLAND
Characterisation of the rhythmic hepatic proteome in mouse liver.

Hepatic proteome rhythmicity in health and disease : it's all about post-translational modifications.

ALBANO MELI
PHYMEDEXP, INSERM U1046 - CNRS UMR9214, MONTPELLIER FRANCE
Patient-specific hiPSC-derived cardiomyocytes, disease modeling and drug screening.

KYLE MINCHAM
TELETHON KIDS INSTITUTE, PERTH AUSTRALIA
Reduced susceptibility to allergic airways disease in BALB/c offspring following maternal therapeutic immunomodulator (OM85) treatment during gestation.

ANYA JONES
TELETHON KIDS INSTITUTE, PERTH AUSTRALIA
Asthma as a Systemic Disease - Activation of inflammatory cells during asthma exacerbations is initiated prior to their migration to the lung.

CHRISTOPHE MOREAU
INSTITUT DE BIOLOGIE STRUCTURALE UMR5075 CEA-CNRS-UGA - GRENOBLE FRANCE
Artificial ligand-gated ion channel created by fusion of G protein-coupled receptors to a potassium channel.

THIERRY PEDRAZZINI
UNIVERSITY OF LAUSANNE MEDICAL SCHOOL, SWITZERLAND
Enhancer-associated long noncoding RNAs in cardiac development and disease.

ÉRIC RHEAUME
INSTITUT DE CARDIOLOGIE DE MONTRÉAL, CANADA
Étude du rôle de l'adénylate cyclase de type 9 (ADCY9) dans l'athérosclérose chez la souris.

GABRIEL RINKEL
UMC UTRECHT, BRAIN CENTER RUDOLF MAGNUS, THE NETHERLANDS
From clinic to research to clinic: screening for and management of unruptured intracranial aneurysms.

SÉBASTIEN ROGER
INSERM U1069 NUTRITION, CROISSANCE ET CANCER, TOURS, FRANCE
Pore-forming and auxiliary subunits of voltage-gated sodium channels (NaV) in cancer cells: Complementary effects in the development of metastases ?

VIOLAINE SAINT ANDRE
POST-DOCTORANTE, UMR CNRS 3244 / UPMC, FRANCE
Models of Human Core Transcriptional Regulatory Circuitries.

AURÉLIEN SERANDOUR
ECOLE CENTRALE, CRCINA, NANTES FRANCE
Epigenomics and high-throughput single-cell transcriptomics: powerful tools to understand cancer initiation and progression.

WATARU SHIMIZU
NIPPON MEDICAL SCHOOL, TOKYO JAPAN
Genotype-phenotype correlation in inherited arrhythmias syndromes.

OLGA SOKOLOVA
UNIVERSITÉ D'ETAT LOMONOSOV, MOSCOW RUSSIA
Obtaining the ion channel high resolution structures by electron cryo-microscopy.

MAURO TURRINI
INSTITUT DES ETUDES AVANCÉES DE NANTES, FRANCE
L'ADN sur Internet: significations et valeurs de données personnelles au sein de la génomique personnelle.

EXTERNAL SEMINARS 2018

HUGUES ABRIEL
UNIVERSITÉ DE BERN, SWITZERLAND
TRPM4 Channel in Cardiac Conduction Disease.

ONNIK AGBULUT
INSTITUT DE BIOLOGIE PARIS-SEINE (IBPS), UMR CNRS 8256, FRANCE
Cardiac tissue engineering for medical applications.

CONNIE BEZZINA
DEPARTMENT OF CLINICAL AND EXPERIMENTAL CARDIOLOGY, AMSTERDAM, PAYS-BAS
Genome-wide association study in probands with Long QT Syndrome.

ERICA DAVIS
DUKE UNIVERSITY MEDICAL CENTER, DURHAM, NC, USA
Functional dissection of pediatric genetic disease.

SIMON DUCHEIX
INSTITUTO TUMORI "GIOVANNI PAOLO II" IRCCS / UNIVERSITÀ DI BARI, ITALIE
Ablation of Stearoyl-CoA Desaturase-1 in the intestinal epithelium drives gut inflammation and tumorigenesis that are rescued by dietary oleate.

HÉLÈNE DUEZ
UMR1011 INSERM - INSTITUT PASTEUR DE LILLE - EUROPEAN GENOMIC INSTITUTE FOR DIABETES (EGID), FRANCE
Rev-erbα: a regulator of circadian physiology.

HODAKA FUJII
HIROSAKI UNIVERSITY GRADUATE SCHOOL OF MEDICINE, HIROSAKI, JAPAN
Biochemical analysis of chromatin mechanisms using the locus-specific chromatin immunoprecipitation technology.

VÉRONIQUE GEBALA
NATURE COMMUNICATIONS, SPRINGER NATURE - GERMANY
Publishing in Nature Research journals: tips from the Editor.

CHARLOTTE GLINGE
DEPARTMENT OF CARDIOLOGY, RIGSHOSPITALET, COPENHAGEN, DENMARK
Meta-Analysis of Genome Wide Association Studies of Ventricular Fibrillation during first acute Myocardial Infarction.

HECTOR VALDIVIA
CARDIOVASCULAR RESEARCH CENTER À L'UNIVERSITÉ DU WISCONSIN, MADISON, USA
Scorpions, snakes, insecticides and coffee: new insights into the mechanisms of calcium-dependent arrhythmias.

ELINA IKONEN
UNIVERSITY OF HELSINKI, FINLAND
Lipid droplet biogenesis: role of seipin.

FLORIAN LESAGE
IPMC, VALBONNE, FRANCE
Canaux potassiques à deux domaines pore: propriétés fonctionnelles et intérêt thérapeutique.

PHILIPPE LORY
IGF, MONTPELLIER, FRANCE
Calcium et Phosphorylation: Deux mécanismes interdépendants pour moduler l'activité des canaux calciques de type T.

NAOMASA MAKITA
DEPARTMENT OF MOLECULAR PHYSIOLOGY, NAGASAKI, JAPAN
Cardiac Emerinopathy, Novel Non-syndromic X-linked Left Ventricular Noncompaction Associated with Progressive Atrial Conduction Disturbance.

MICHAEL MARKL
NORTHWESTERN UNIVERSITY, FEINBERG SCHOOL OF MEDICINE & MCCORMICK SCHOOL OF ENGINEERING, CHICAGO, USA
Aortic Valve Disease and Aortopathy: New Insights from 4D flow MRI.

GANNA PANASUYK
INSERM U1151/CNRS UMR 8253, NECKER ENFANTS MALADES INSTITUTE (INEM),
Growth and Metabolic Control by PI3K Signalling.

LAURENT REBER
INSERM U1222, INSTITUT PASTEUR, PARIS, FRANCE
Deciphering the contribution of antibody subclasses, Fc receptors and myeloid cells in allergic shock.

ANTOINE RIMBERT
UNIVERSITAIR MEDISCH CENTRUM GRONINGEN, THE NETHERLANDS
Towards the identification of novel regulators of plasma lipid levels.

SALVATORE SPICUGLIA
TECHNOLOGICAL ADVANCES FOR GENOMICS AND CLINICS (TAGC), INSERM U1090, MARSEILLE
Assessment of enhancer activity by high-throughput reporter assays: Identification of core promoters with distal enhancer functions.

RAFIK TADROS
MONTREAL HEART INSTITUTE, CANADA
Genome-wide association study in hypertrophic cardiomyopathy provides novel insights on disease mechanism.

PIERRE-LOUIS THARAUX
PARIS CARDIOVASCULAR CENTRE - PARCC, FRANCE
Disease Tolerance as a Defence Strategy against Renal Microvascular Disease.

MARIE VERBANCK
ICAHN SCHOOL OF MEDICINE AT MOUNT SINAI, NEW YORK, USA
The landscape of horizontal pleiotropy in human genetic variation.

NORBERT WEISS
INSTITUTE OF ORGANIC CHEMISTRY AND BIOCHEMISTRY, PRAGUE, CZECH REPUBLIC
Trafficking of T-type calcium channels in health and disease.

SCIENTIFIC EVENTS

Lab members also organize or co-organize congresses and symposia with colleagues from others institutions.

2017

"PRINTEMPS DE LA CARDIOLOGIE"
NANTES, FRANCE

24TH MEETING OF THE FRENCH SOCIETY OF TOXINOLOGY (SFET)
PARIS, FRANCE

"LA FOLLE JOURNÉE DE L'ANÉVRISME"
NANTES, FRANCE

2018

"MÉDECINE GÉNOMIQUE DES MALADIES COMMUNES" – VACARME SYMPOSIUM
NANTES, FRANCE

"9E ASSISES DE GÉNÉTIQUE HUMAINE ET MÉDICALE"
NANTES, FRANCE

ANNUAL MEETING OF "SOCIÉTÉ FRANCOPHONE DU DIABÈTE"
NANTES, FRANCE

"PRINTEMPS DE LA CARDIOLOGIE"
MONTPELLIER, FRANCE

25TH MEETING OF THE FRENCH SOCIETY OF TOXINOLOGY (SFET)
PARIS, FRANCE

"LA FOLLE JOURNÉE DE L'ANÉVRISME"
NANTES, FRANCE

PREPARING FOR THE FUTURE

PREPARING FOR THE FUTURE

L'institut du thorax has been particularly attractive to young investigators for the last two years, with the recruitment of 8 talented postdocs from abroad.

Three of them obtained research grants to set up their own programs. Their profiles illustrate how our laboratory prepares for the future by promoting early career development ◆

WIENEKE DIJK

***"AIDE AU RETOUR EN FRANCE – 2016"* — FRM POST-DOCTORAL FELLOWSHIP**
2017-2019 : 100 K€

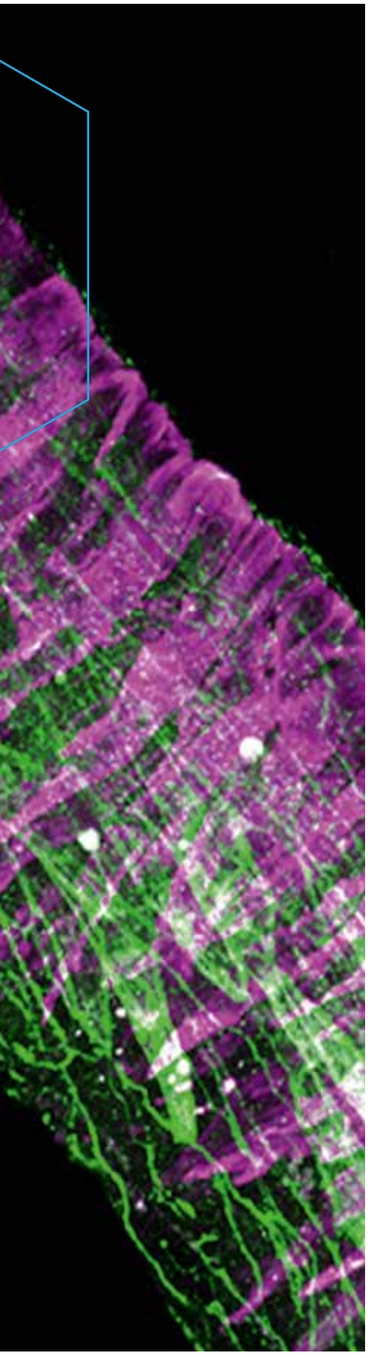
Wieneke Dijk is a Dutch post-doctoral researcher specialized in the molecular regulation of lipoprotein metabolism. She obtained her PhD in 2016 at Wageningen University in the Netherlands under the supervision of Sander Kersten, as part of a transatlantic network of excellence on triglyceride metabolism funded by the Leducq foundation. During her PhD, she worked on the mechanisms regulating the intravascular lipolysis of triglyceride-rich lipoproteins in the adipose tissue, using a variety of in vitro and in vivo techniques. She then joined *l'institut du thorax* to work on hepatic lipoprotein metabolism and to add a clinical perspective to her work.

Focus on understanding the molecular mechanisms that contribute to the development of atherogenic dyslipidemia.

Team IV - Dyslipidemia and lipotoxicity (Bertrand Cariou)

Atherogenic dyslipidemia, a condition frequently found in insulin-resistant and/or type 2 diabetic patients, represents a major and independent cardiovascular risk factor. Atherogenic dyslipidemia is characterized by elevated triglyceride levels and decreased HDL ('good') cholesterol levels. A key factor triggering atherogenic dyslipidemia is the increased production of triglyceride-rich very low-density lipoproteins (VLDLs) by the liver. Multiple observations have suggested a role for PCSK9 – a protein well known to increase LDL cholesterol levels – in hepatic VLDL secretion, but the underlying mechanisms remain unclear. To clarify this role of PCSK9, Wieneke uses various state-of-the-art techniques, including hepatocyte-like cells derived from inducible pluripotent stem cells and CRISPR-Cas9. She also set up an innovative mass-spectrometry-based approach called BioID at l'institut du thorax to identify what proteins might collaborate with PCSK9 to promote VLDL secretion in collaboration with Prof. Coulombe at the IRCM in Montréal. Besides PCSK9, Wieneke works on the implication of other proteins in atherogenic dyslipidemia together with the teams of Dr. Sauzeau at l'institut du thorax and Dr. Di Philippo in Lyon.
With her studies, Wieneke aims to provide new insights into the molecular pathways that regulate VLDL secretion by the liver and that contribute to the development of atherogenic dyslipidemia. By clarifying the roles of PCSK9 and other proteins, she hopes to open up new therapeutic avenues to improve the clinical management of atherogenic dyslipidemia.

From left to right:
Romain Capoulade
Anne-Clémence Vion
Wieneke Dijk



ANNE-CLÉMENCE VION

***"AIDE AU RETOUR EN FRANCE – 2017 "* — FRM POST-DOCTORAL FELLOWSHIP**
2018-2020: 134 K€

***"NEXT JUNIOR TALENT – 2018 "* — I-SITE NEXT**
2019-2022: 404 K€

Anne-Clémence Vion is specialized in vascular biology with a focus on mechanosensing in endothelial cells. She did her PhD at the PARCC-HEGP, Inserm U970 (Paris, FR) under the supervision of Chantal Boulanger, working on the effect of shear stress on microparticle release by the endothelium and on atherosclerosis development. Then, she moves toward development, joining Holger Gerhardt laboratory (CRUK, London, UK ; Max Delbrück Center, Berlin, DE) to investigate the role of shear stress in vascular patterning during angiogenesis. She came back to France, in Gervaise Loirand's Team III at *l'institut du thorax*, with the will of keeping her interest in mechanotransduction and come back to its pathophysiological aspect.

Focus on the role of hemodynamic forces applied on the vascular wall in the pathogenesis of intracranial aneurysm.

Team III - Signaling in vascular and pulmonary pathophysiology (Gervaise Loirand)

Intracranial aneurysm is an asymptomatic cerebrovascular abnormality affecting 3% of the general population, the rupture of which leads to death or severe disability. The mechanisms underlying its formation, growth and rupture are still mostly unknown. There are no reliable diagnostic tools to predict the formation and the fate of an intracranial aneurysm, and no pharmacological drugs to prevent its rupture. A defective adaptation of the vascular cells to local extreme mechanical stresses seems to be a key step in the initiation of the lesion. To properly respond to hemodynamic forces, vascular cells transform a mechanical stimulus in a chemical signal. The actin cytoskeleton, mainly controlled by the Rho family of small G-proteins, is a key player of the mechanosensing system. Unfortunately, their regulation and the regulation of their activators, the RhoGEFs, by hemodynamic forces is largely unknown.

Anne-Clémence hypothesized that Rho protein signaling is involved in the maladaptive response of intracerebral arteries to hemodynamic forces. The goals of her project are thus to identify the RhoGEFs regulated by mechanical stresses in endothelial and smooth muscle cells of cerebral arteries, to assess their physiological role and their implication in the development of intracranial aneurysm. She aims to provide new insights into the molecular mechanisms leading to intracranial aneurysm formation, with the prospect of discovering new diagnostic and therapeutic tools with preventive and curative potentials.

ROMAIN CAPOULADE

EUROPEAN RESEARCH AREA NETWORK (ERA-NET) ON CV DISEASES, EUROPEAN FRAMEWORK PROGRAM FOR RESEARCH AND INNOVATION — 'HORIZON 2020' EUROPEAN COMMISSION

PICASSO PROJECT — COORDINATOR: PAOLO POGGIO, MILAN, ITALY
2019-2022 : 250 K€

***"CONNECT TALENT 2017"* — PAYS DE LA LOIRE REGIONAL COUNCIL**
2018-2023: 502 K€

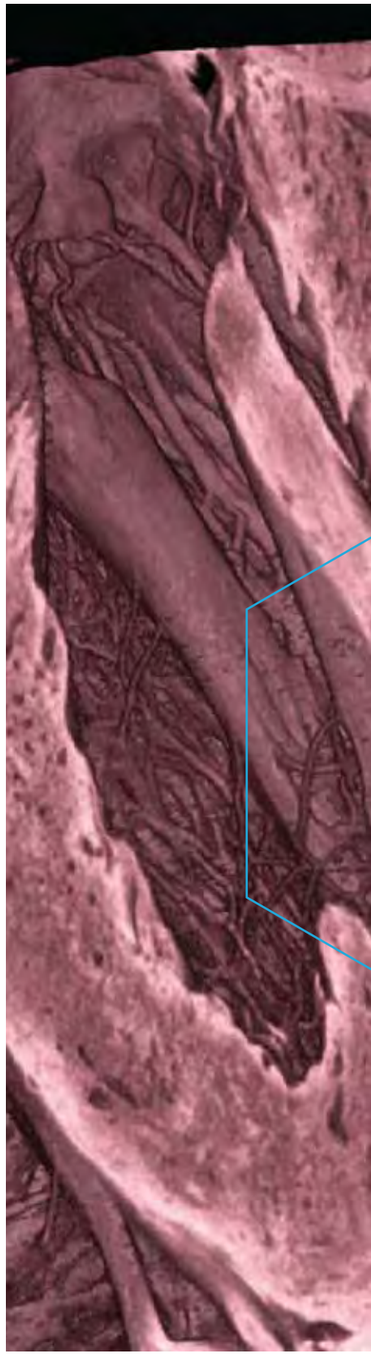
FELLOWSHIP, INSTITUT DE FRANCE, FONDATION LEFOULON-DELALANDE
2017-2018: 57 K€

Romain Capoulade is a research scientist working on the pathophysiology of heart valve diseases, with the main objectives to decipher mechanisms associated with development of these diseases and identify potential therapeutic targets to treat them. He did is PhD in the laboratory of Philippe Pibarot at the *Institut Universitaire de Cardiologie et de Pneumologie de Québec* at the Laval University (Quebec, CA). His research program was focused on the identification of metabolic determinants of the progression of aortic stenosis. Then, he joined in 2014, the research laboratory of Judy Hung at the *Massachusetts General Hospital (MGH) — Harvard Medical School* in Boston for a 3-year post-doctoral fellowship. Benefiting of the exceptional environment provided by the Harvard Medical School, he focused his research on mitral valve diseases. These international training experiences in two worldwide recognized institutions allowed him to develop expertise on multimodality imaging dedicated to a better understanding of valve diseases. At the *institut du thorax*, he joined the team of Jean-Jacques Schott who identified genetics components of heart valve diseases, such as mitral valve prolapse or aortic valve stenosis, to work on the impact of these identified genes in these pathologies.

Focus on understanding the pathophysiological mechanisms involved in the development of valvular heart diseases.

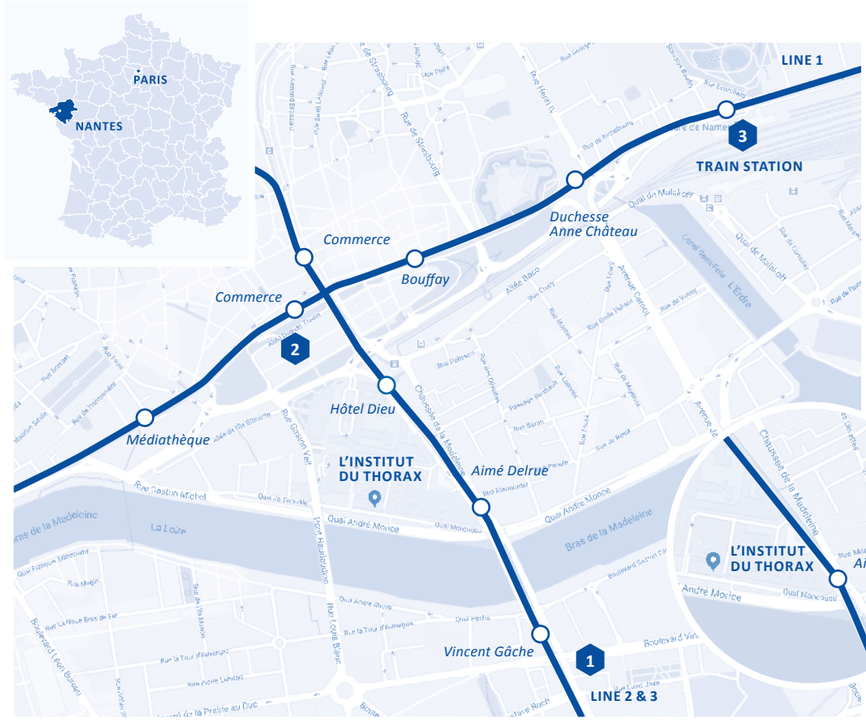
Team I : Cardiovascular Genetics (Jean-Jacques Schott)

Valvular heart diseases are a major cause of cardiovascular morbidity and mortality in developed countries. Aortic and mitral valve diseases are the most frequent. There is currently no medical therapy available for heart valve diseases and the only option for the patients suffering from these relatively frequent diseases are open heart surgery or transcatheter valve implantation.
Initially, valvular heart diseases were defined as purely degenerative processes. However, in the last decades, several clinical and experimental studies have provided evidence that pathophysiological mechanisms are involved in the development and progression of these diseases. This shift has open new avenue to study heart valves biology. At the *institut du thorax*, the team led by Jean-Jacques Schott aims to decipher the genetic architecture of valvular heart diseases. The team has identified for the first time, genes associated with valvular heart diseases. The team has identified for the first time, genes associated with valvular heart diseases.
Romain aims to develop research projects focused on the underlying pathophysiological mechanisms associated with the presence of mutations in these genes. His program relies on the study of animal models (a unique knock-in rat model for a mutation on the *FLNA* gene associated with the development of mitral valve prolapse generated by the team or the PCSK9 knock-out mice). This approach, coupled with the analysis of patients that suffer from these diseases, offers a unique opportunity to decipher molecular and cellular mechanisms associated with the development of mitral valve prolapse or the role of PCSK9 in the development of aortic stenosis. Multimodality and multiscale imaging is the cornerstone of these programs offering a comprehensive and reliable phenotyping of the animal models and humans.



CONTACT & ACCESS MAP

Sixth largest city in France, Nantes is located between the Loire Valley and Brittany, 30 minutes from the ocean. Close to Paris (2 hours by TGV) and European capitals (2 hours by plane), Nantes has an urban population among the youngest in France (2/3 of the inhabitants are under 40 years old).



1 TRAMWAY
Line 2 and 3 – "Aimé Delrue" station

2 AIRPORT/CITY CENTRE SHUTTLE
Departure every 20 minutes. Stop at "Commerce" station and take line 2 or 3 and stop at "Aimé Delrue" station.

3 TRAIN
Less than 2 hours from Paris Montparnasse. The TGV train station is located in the city centre. North exit: tramway line 1, Stop at "Commerce" station and take line 2 or 3 and stop at "Aimé Delrue" station.

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