Summary

Identity Card

UMRS 1166 – ICAN
Cardiovascular Diseases and Metabolism

Faculté de médecine – Site Pitié-Salpêtrière
91 boulevard de l'hôpital
75013 Paris - France

www.insermu1166.fr

UMRS 1166-ICAN was created in 2014. It is directed by Stéphane Hatem.

The second quinquennium of the unit is composed by 5 teams:

- Genomics and Physiopathology of Myocardial Diseases, Philippe Charron
- Atherothrombosis and Applied Pharmacology, Jean-Philippe Collet
- Molecular and Cellular Plasticity in Cardiovascular Diseases, Sophie Nadaud and Elise Balse
- Cellular and Systemic Lipid Metabolism, Wilfried Le Goff
- Mononuclear Phagocytes in Cardiometabolic Diseases, Philippe Lesnik

UMRS 1166 – ICAN STAFF

- 135 permanent positions and non-permanent staff:
  - 70 permanent researchers (Inserm, CNRS, Sorbonne University)
  - 4 post-doctoral fellows
  - 19 PhD students
  - 24 permanent engineers and technicians
  - 9 non-permanent engineers and technicians
  - 9 undergraduates

CORE FACILITIES AND KEY TECHNOLOGIES ON SITES

- Cardiovascular Function Exploration Facility - Nathalie Mougenot
- P3S – Genomics Platform - UMS 37 PASS - Stéphane Le Crom
- CyPS - Flow cytometry Platform Catherine Blanc
- Small animal (mouse, rat) models of CV diseases – Functional Experimental Center – UMS 28 – Serban Morosan
- IHU ICAN technical platforms, Ludovic Le Chat
  - preclinICAN : Mouse Cardiometabolism Thierry Huby, Amélie Lacombe
  - ICAN Imaging: Cardiovascular MRI and Image Analysis – Alban Redheuil, Khaoula Bouazizi
  - Bio ICAN : Biological Resource Center (CRB) – Sara Cipriani (ISO 9001)
  - ICAN Human Hep Cell : Tissue and Hepatic Cells Building – Chantal Housset and Filomena Conti, Lynda Aoudjehane
  - Cyto-ICAN : Cells Analysis Sorting – Sébastien André, Florence Deknuydt
  - ICANalytics Lipidomic – Anatol Kontush – Marie Lhomme
  - ICANalytics Metabolomic – Philippe Lesnik , Farid Ichou
  - iPSICAN : iPS differenciation platform – Eric Villard, Vincent Fontaine
  - ICAN Integromics – JD Zucker, Edi Prifti

Director's introduction

UNIT STRATEGY

Stéphane Hatem

Created in 2014 and renewed in 2019, UMRS 1166 brings under the same umbrella 5 independent teams dedicated to the research on cardiovascular and metabolic diseases, with internationally recognized and complementary expertise in genomics, biostatistics, molecular and cell biology, physiology and pharmacology. The UMR is located in the School of Medicine of Pitié-Salpêtrière Hospital, one of the largest teaching hospital-research site in France and among the largest ones in Europe. In the past 15 years, the site has seen major growth and investments into heart, vascular and metabolic research coupled with a parallel growth in fundamental research efforts. The campus has also developed the requisite platforms to perform modern molecular, cellular, physiological and systems biology. An Inserm clinical investigation centre provides a bridge between basic and clinical researches. The unit has played a major role in the creation of the IHU-ICAN (Institut Hospitalo-Universitaire-Institute of Cardiovascular and Nutrition Diseases), one of the 6 IHU created in France. IHU-ICAN has provided unique core facilities for clinical research and human bio-resources in the field of cardiovascular and nutrition diseases. We are also a member of the *Fédération des Recherches Interdisciplinaires Pitié-Salpêtrière:* 4 research units, 400 researchers and staff, core facilities mutualization, multidisciplinary scientific life.

Our scientific project is organized around four main axes which are the stakeholders of our campus and by which we have done significant scientific contributions. These include atherothrombosis and coronary diseases, genomics of cardiomyopathies and heart failure, atrial fibrillation and cardiac arrhythmias, lipids and atherosclerotic vascular diseases.
Cardiovascular diseases and metabolic disorders, two major causes of death and morbidity share pathophysiological features. Most often cardiovascular and metabolic diseases are due to multiple factors including nutrition, lifestyle, environment, genetics and epigenetics that operate at the initiation of the disease and/or during its progression. Cardiovascular diseases and metabolic disorders result from evolving processes that affect a multiple pathways at the tissue, organ and inter-organ level sharing common initial pathways and dysfunctions. The "silent" nature of their initial evolution results in diagnosis at a late-stage following stroke, myocardial infarction, heart failure or sudden death. Therefore, our 2 major goals are 1/ to identify new individual phenotypes with shared pathways that will be targeted for intervention as well as integrate the multifactorial and multi-organ nature of these disorders and 2/ the identification of the earliest molecular and cellular stages, which would allow early prevention to delay the occurrence of the disease or of its complications. In addition, the challenge of research in cardiovascular and metabolic diseases is to integrate the large amount of data and information generated by the various domains of research in schemes that are translatable and relevant to pathophysiology of these diseases. To achieve these aims, UMRS 1166 has developed multidisciplinary and integrated research approaches together with tight links with clinical research and access to unique human bio-resources and patient cohorts.

>

Team 1

GENOMICS AND PATHOPHYSIOLOGY OF MYOCARDIAL DISEASES : FROM MONOGENIC TO COMPLEX DISEASES

THE TEAM

TEAM LEADER

Philippe CHARRON, *MD, PhD, PU-PH, AP-HP*

INVESTIGATORS

Flavie ADER, *CCA AP-HP*
Isabelle DENJOY, *MD, PH, AP-HP*
Fabrice EXTRAMIANA, *MD, PhD, MCU-PH, AP-HP*
Véronique FRESSART, *MD, PhD, PU-PH, AP-HP*
Christian FUNCK-BRENTANO, *MD, PhD, PU-PH AP-HP*
Estelle GANDJBAKHCH, *MD, PhD, PH, AP-HP*
Sophie GARNIER, *PhD, MCU, SU*
Pascale GUICHENEY, *PhD, Emerita*
Richard ISNARD, *MD, PhD, PU-PH, AP-HP*
Antoine LEENHARDT, *MD, PhD, PH, AP-HP<*
Julie PROUKNITZKY, *CCA SU*
Nathalie NEYROUD, *PhD, CR, Inserm*
Ewa NINIO, *PhD, Emerita*
Pascale RICHARD, *MD, PhD, PH, AP-HP*
Joe-Elie SALEM, *MD, PhD, MCU-PH, AP-HP*
Eric VILLARD, *PhD, IR, AP-HP*
Noël ZAHR, *MD, PhD, PU-PH, AP-HP*

TECHNICAL ASSISTANTS

Laetitia DUBOSCQ-BIDOT, *T, AP-HP*
Céline de FLORI, *AI IHU ICAN*
Vincent FONTAINE, *PhD, IR, IHU-ICAN*
Arnaud LECLERQ, *T, Inserm*
Sibylle MARTEAU, *AI IHU ICAN*
Claire PERRET, *IE, Inserm*
Lieng TAING, *IR SU*

POST-DOCTORAL FELLOWS

Pierre BOBIN, *PhD, SU*

PHD STUDENTS

Marine FERRAND
Marie GIZON
Océane PIEDALLU
Laetitia RIALLAND

OBJECTIVES

CLINICAL AND SCIENTIFIC CONTEXT OF THE RESEARCH PROJECT

Cardiomyopathies and channelopathies, which constitute the two major subgroups of hereditary cardiac diseases, are the leading causes of sudden cardiac death and heart failure in young patients (<40 years) especially in athletes. Despite improvement in the management of these diseases, through pharmacological drugs, devices and heart transplant, new knowledge about underlying genetic causes, pathways and pathophysiology is required to identify new therapeutic targets or strategies and to better prevent the devastating complications of these diseases.

Moreover, recent advances about the causes of these diseases (especially sarcomeric and ion channel genes variants) led to a new understanding of the complex interplay between genetic architecture (rare and frequent variants) as well as interactions with environmental factors (such as sport, myocarditis, drugs) or gender. This new knowledge and paradigm has important consequences for the global understanding of the physiology of sarcomeric proteins and ion channels as well as for the pathophysiology of complex diseases such as heart failure and arrhythmia.

For more than 15 years our group has been involved in deciphering the genetic and cellular mechanisms underlying the development of cardiomyopathies and channelopathies. We have recently identified new rare or frequent genetic variants involved in these diseases through genome wide association or sequencing strategies. Underlying signaling pathways are studied and new therapeutic approaches are starting based on the new knowledge. Meantime, translational approaches including genetic testing and high throughput resequencing have been developed in clinical practice in order to improve medical management of patients and their families through personalized medicine.

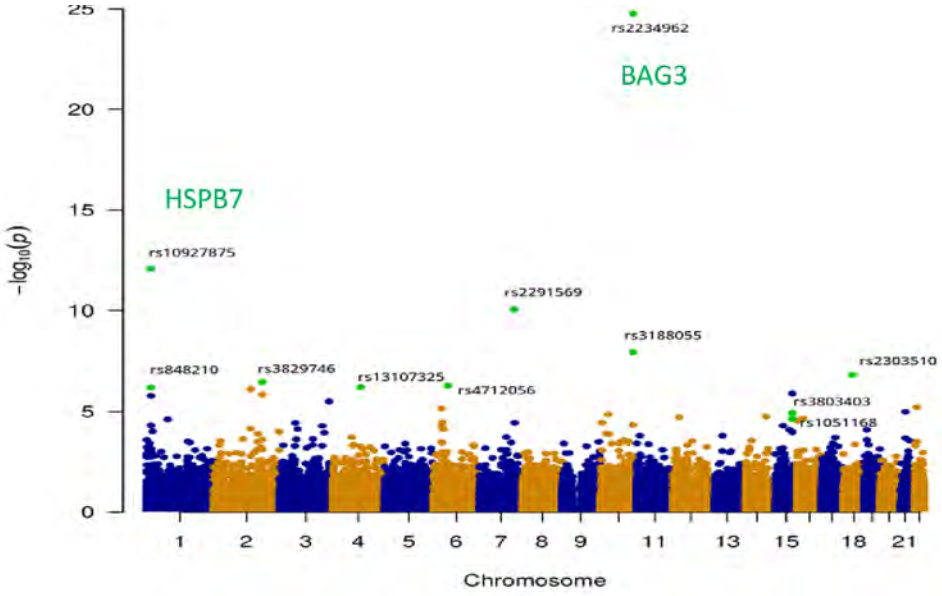
Philippe Charron

RESEARCH PROJECTS

THEME 1 – GENOMICS OF HEART FAILURE DUE TO DILATED CARDIOMYOPATHY

E. VILLARD, S. GARNIER, R. ISNARD, PH. CHARRON

Background. Dilated cardiomyopathy is a complex disease with both familial and sporadic forms. Unraveling the genetic component of this disease to improve patients' care and find new therapeutic targets is one on the leading task of our team. In familial forms, the linkage analysis/positional candidate gene strategy has been developed (Sylvius N, 2001), completed now by next generation exome and genome sequencing. For sporadic forms, the candidate gene strategy was quite unfruitful and, rapidly, we turned to high throughput association studies on thousands of cases and controls. Successive GWAS on pooled DNA samples (Villard E, 2011) or using exomic enriched SNPs (Esslinger U, 2017) revealed 8 candidate genomic loci (HSPB7, TTN, SLC39A8, MLIP, FLNC, BAG3, ALPK3 and FHOD3), two being also implied in Ischemic Heart Failure (Garnier S, 2015). A third GWAS on 2,700 sporadic DCM cases and 4,400 controls, combined with an imputation analysis, is now ongoing to identify new susceptibility loci.



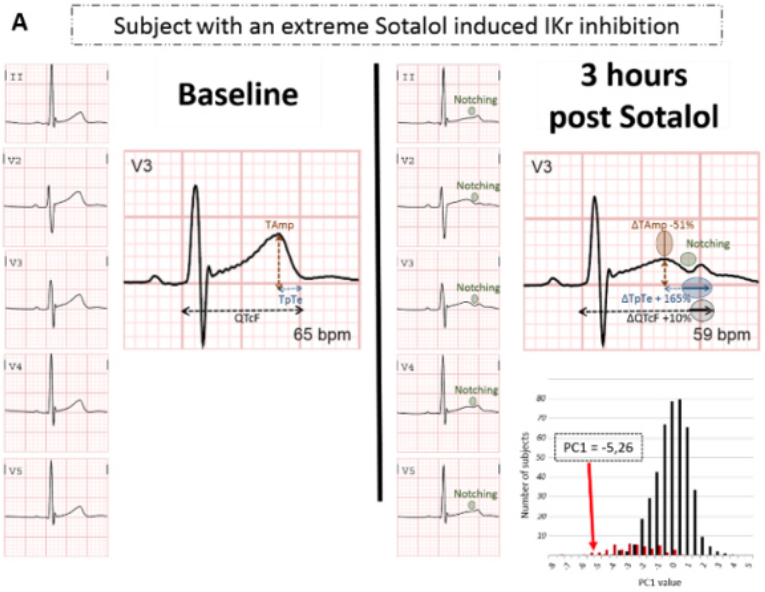
Manhattan Plot - Exome Wide Association Study. 95,499 variants were investigated by logistic regression analysis. Associations are summarized in the Manhattan plot which displays (green dots) the eleven SNVs significantly associated with DCM. From Esslinger U et al., 2017.

Our team is also deeply implied in the pathophysiological impact of the discovered genes. Based on our results from GWAS/EWAS in DCM we hypothesize that protein quality control, in the context of repeated mechanical stress, is a major pathway for cardiomyocytes health. Such hypotheses, and potential therapeutic applications, are questioned using knock-in mouse models of DCM and iPs-derived cardiomyocytes with Engeniered Heart Tissue (EHT) cultured from mutated patient's cells. We also initiated a collaborative project with pharmaceutical industry whose purpose is to identify the molecular pathways implicated in hypertrophic cardiomyopathy and perform molecular screen based on iPS-derived cardiomyocytes. We take advantages from our strong anchoring within the national referral centre for cardiac hereditary diseases and unique access to the patients and their genotypes, the in-house facility dedicated to iPS-cardiomyocytes and our skills in genomic editing.

THEME 2 - GENOMIC ANALYSIS OF ABNORMAL CARDIAC REPOLARIZATION RESPONSE TO PHARMACOLOGIC DRUGS

J.E. SALEM, C. FUNCK-BRENTANO

Many drugs used for non-cardiovascular and cardiovascular purposes, such as sotalol, have the side effect of prolonging cardiac repolarization, which can trigger life-threatening cardiac arrhythmias by inhibiting the potassium-channel IKr (KCNH2). ECG changes (such as QTc, Tpeak-Tend, Tamp, T wave notches) vary markedly between subjects, suggesting the existence of predisposing genetic factors. In the GENEREPOL study, 990 healthy individuals, prospectively challenged with an oral sotalol dose, were monitored for changes in ventricular repolarization on ECG. QTc and TpTe increased and TAmp decreased. A random subsample of 489 individuals were subjected to a genome-wide-association analysis where 8,306,856 imputed single nucleotide polymorphisms (SNPs) were tested for association with QTc, TpTe and TAmp modulations (D), as well as their derived principal-components, and notches apparition. None of the studied SNPs reached the statistical threshold (Salem JE et al, 2017). The study, however, showed that a principal component analysis based on DQTcF, DTAmp and DTpTe might be an integrative way to further differentiate patients with the most extreme IKr inhibition. We patented this diagnostic algorithm in 2016 as a method of determining the susceptibility for induction of a torsade de pointes (PCT/EP2017/058714, BRV 116 - WO -- 2016-096).



The PC1 values and distribution of discovery cohort are shown. PC1 is issued from principal component analysis of ΔQTc, ΔTpTe and ΔTAmp. «Notcher» subjects are represented in red and «non notcher» in black.

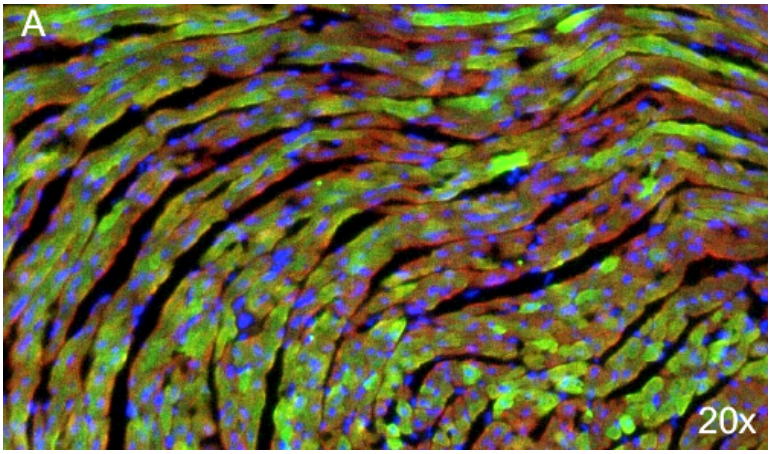
Typical QT and T-wave changes (A) in a subject with a pronounced sotalol-induced IKr Inhibition indicated by a notch and (B) in a subject with minimal sotalol-induced IKr Inhibition.

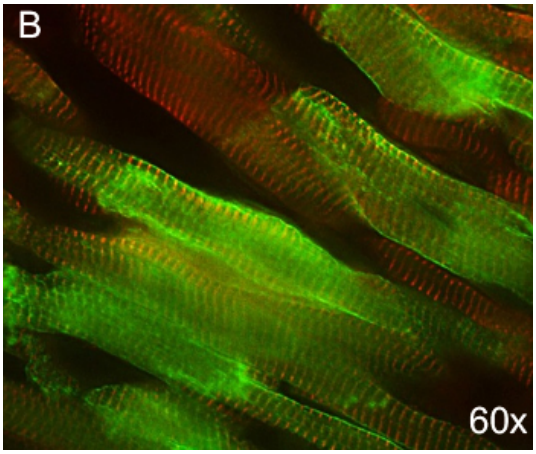
Our current project is to understand the determinants of gender specific repolarization. Cardiac repolarization is influenced by complex interactions between sex steroid hormones and gonadotropins (Salem JE et al, 2016), depending on gender. We recently showed that the progesterone/estradiol ratio in women, testosterone in men, and FSH in both genders are major determinants of ventricular repolarization (Abehsira G & al, 2016). We are planning to further study in GENEREPOL cohort the influence of sex, hormones on drug induced QT prolongation, combined with the used of whole-exome sequencing seeking for rare and low frequency variants. We will also seek for interaction between hormones and expression of genes using cardiomyocytes derived from iPs cells of patients with congenital or drug-induced long QT syndrome. We plan to test if an appropriate exogenous hormonal administration might increase the repolarization reserve in situation at risk. We already patented a method of treatment of "torsades de pointes" by exogenous hormonal administration (PCT/EP2017/059097, BRV 119 - WO -- 2016-120).

THEME 3 - FROM DECIPHERING THE GENETIC DETERMINANT OF VENTRICULAR ARRHYTHMIA TO THERAPEUTIC APPLICATIONS

N. NEYROUD, F. EXTRAMIANA, A. LEENHARDT, P. GUICHENEY

Our group has been interested for many years in deciphering the genetic background of cardiac channelopathies (Blancard M 2018, Clatot J 2012). The SCN5A gene encodes the human cardiac Na^+ channel $^+$-subunit, Nav1.5, responsible for initiation and propagation of the action potential. Loss-of-function mutations in SCN5A have been linked to life-threatening cardiac arrhythmias (such as the Brugada syndrome or sick sinus syndrome (Ziyadeh-Isleem A, 2014)). A murin model of Scn5a haplo-insufficiency has been developed, partially recapitulating the Brugada syndrome phenotype. Our project sought to overexpress the cardiac Na^+ channel in Scn5a+/- deficient mice in an attempt to restore their Na^+ current and their ECG parameters. As a consequence of the large size of the SCN5A gene, we have developed a dual AAV vector strategy to produce two AAV9 populations allowing, *in vivo*, the translation of the full hSCN5A gene fused to the gfp gene as a reporter. Eight weeks after systemic AAV-injection in mice, our results show a robust transduction of cardiac cells, a normalization of the PR interval on injected-mice ECGs, and a significant increase of the Na^+ current in transduced myocytes (N. Doisne & al., manuscript in preparation). These results will give impulse to gene therapy strategies of malignant arrhythmias observed in SCN5A loss-of-function-related channelopathies.





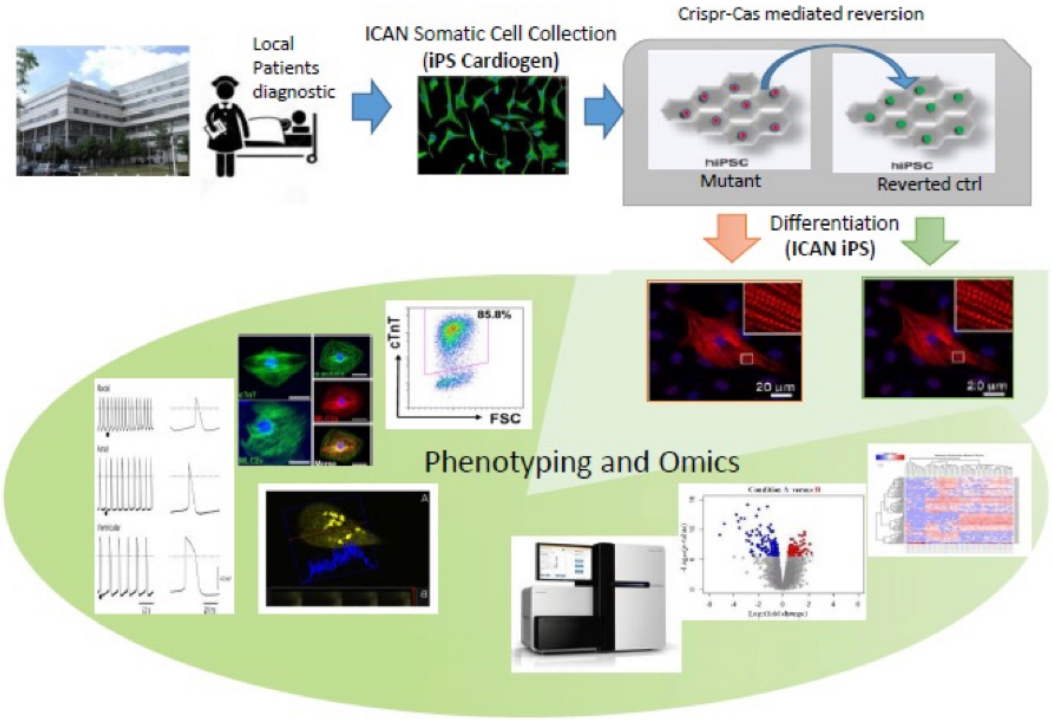
Eight-micrometer slices of heart tissue from a mouse injected with the AAV carrying hSCN5A. AAV injection led to the expression of Nav1.5 tagged with the GFP in almost 50% of heart cells. A. Nuclei are stained in blue, α-actinin in red and the GFP in green (20x). B. Magnification of transduced cardiomyocytes (60x).

Idiopathic Ventricular Fibrillation (IVF) is a rare cause of sudden cardiac arrest. The exact incidence of IVF is unknown but is declining with the advance of diagnostic testing and the discovery of primary arrhythmia syndromes (Visser M, 2016). For more than 15 years, our group has worked to investigate patients presenting with ventricular tachycardia and to collect their familial information and DNA. We have recently selected a group of 60 cases diagnosed with IVF originating from Purkinje fibers. All were resuscitated cardiac arrest patients in whom known cardiac, respiratory, metabolic and toxicological etiologies had been excluded. Our project seeks to identify new genes and variants involved in IVF by a whole-exome sequencing approach.

THEME 4 - IDENTIFY NEW PHYSIOLOGICAL PATHWAYS IN ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY USING INNOVATIVE HUMAN CELLULAR MODELS

E. GANDJBAKHCH, E. VILLARD

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a rare inherited cardiomyopathy characterized by fibrofatty replacement of myocytes leading to ventricular arrhythmia, sudden death and heart failure mainly caused by desmosomal genes mutations (Fressard V, 2010). Ongoing work by our team has shown the essential role of cadherin mediated adhesion in the disease (Vite A, 2013 & Vite A, 2019). One major challenge in translational research of ARVC is to generate a pertinent cardiac cellular model expressing mature desmosomes and recapitulating cyclic mechanical load. In this project, we will generate an IPs-derived engineered heart tissue (hIPS-EHT) which will be used as an innovative in vitro model to unravel physiopathology of ARVC and explain the mutation specific phenotypes. This 3D cardiac model reconstitutes a mature contractile cardiac tissue reproducing mechanical stress, as observed *in vivo*. We aim to structurally compare the effect of PKP2 and DSG2 mutations on cardiomyocyte and junction structures using 3D immunofluorescent imaging as well as their consequences on desmosome function and cardiomyocytes electrophysiological properties. We also aim to study the expression profiles associated with PKP2 and DSG2 mutations by whole-transcriptome analysis using high throughput RNA sequencing.

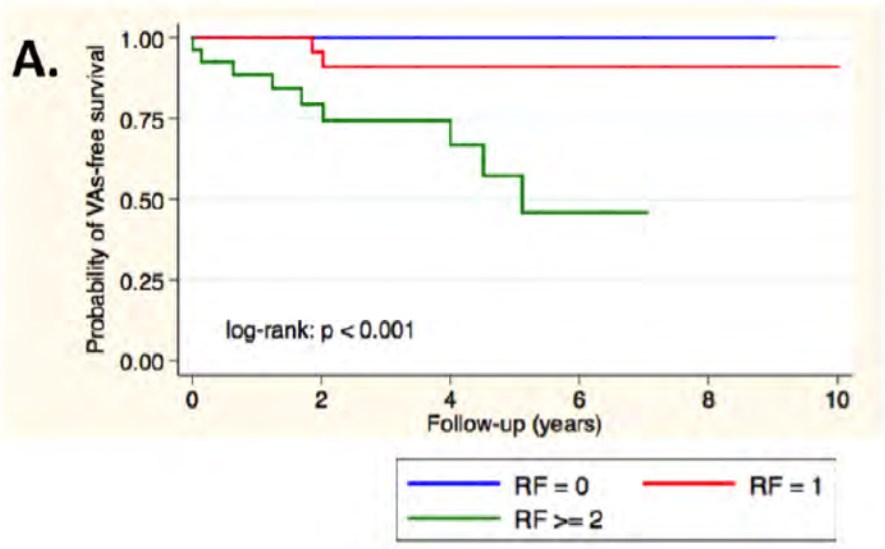


Production of human cardiomyocytes derived from patient iPS cells with mutation of interest

THEME 5 - TRANSLATIONAL IMPACT OF GENETIC TESTING ON PRECISION MEDICINE

P. RICHARD, V. FRESSARD, E. GANDJBAKHCH, PH. CHARRON

Apart from the use of genetic results in the cascade screening of families with hereditary diseases (Charron P, 2010; & Cirino AL, 2017), our team has reported several publications about the role of some genes or mutations in the severity of cardiac diseases, such as the role of multiple mutations on the prognosis of a cardiomyopathy (Richard P, 2002, Fressard V, 2010) or the role of some particular genes such as PRKAG2 & GLA in HCM (Thevenon J, 2016, Séné T, 2016) or DSG2 in ARVC (Hermida A, 2019). Identification of these genetic factors may help to identify high risk profile patients that would benefit from close cardiac monitoring and early treatments such as implantable cardioverter defibrillator or heart failure therapy. An illustrative example of direct personalized therapeutic impact is about defibrillator implantation decision based on genetics. Our team actively participated to international joint efforts to establish the independent prognostic role of LMNA mutation, associated with high risk of sudden death, and to clarify the identification of patients that would benefit most from implantable cardiac defibrillator implantation (van Rijsingen IA, 2012; Kumar S, 2016; Thuillot M, 2019).



First validation of a prognostic score in heart failure due to LMNA gene. Four predictive factors (non sustained ventricular tachycardia, LV Ejection Fraction <45%, male sex and non-missense mutations) for malignant ventricular arrhythmia (VA) were studied in a monocentric cohort. ICD is recommended in the presence of 2 risk factors. From Thuillot M & al., 2019.

Refine the genetic spectrum of cardiomyopathies with high throughput sequencing. Large cohorts of patients with Left ventricle non-compaction (LVNC), HCM and DCM have been collected through the national network of the Referral center for cardiac hereditary diseases. Resequencing strategy with various panels of genes, including a panel of >100 genes involved in various cardiac hereditary diseases are under way in order to refine the prevalence of genes, the overlap between cardiomyopathy subtypes and then progress towards optimal diagnostic strategies for routine care of patients and families.

>

SELECTED PUBLICATIONS

Abehsira G, Bachelot A, Badilini F, Koehl L, Lebot M, Favet C, Touraine P, Funck-Brentano C, Salem JE.
Complex Influence of Gonadotropins and SexSteroid Hormones on QT Interval Duration.
J Clin EndocrinolMetab. 2016 Jul;101(7):2776-84.

Blancard M, Debbiche A, Kato K, Cardin C, Sabrina G, Gandjbakhch E, Probst V, Haissaguerre M, Extramiana F, Hocini M, Olivier G, Leenhardt A, Guicheney P, Rougier JS.
An African loss-of-function CACNA1C variant p.T1787M associated with a risk of ventricular fibrillation.
Sci Rep. 2018 Oct 2;8(1):14619.

Charron P, Elliott PM, Gimeno JR, Caforio ALP, Kaski JP, Tavazzi L, Tendera M, Maupain C, Laroche C, Rubis P, Jurcut R, Calò L, Heliö TM, Sinagra G, Zdravkovic M, Kavoliuniene A, Felix SB, Grzybowski J, Losi MA, Asselbergs FW, García-Pinilla JM, Salazar-Mendiguchia J, Mizia-Stec K, Maggioni AP; *EORP Cardiomyopathy Registry Investigators. The Cardiomyopathy Registry of the EURObservational Research Programme of the European Society of Cardiology: baseline data and contemporary management of adult patients with cardiomyopathies.*
Eur Heart J. 2018 May 21;39(20):1784-1793.

Christensen, A.H., Kamstrup, P.R., Gandjbakhch, E., Benn, M., Jensen, J.S., Bundgaard, H., Villard, E., Tybjærg-Hansen, A.
Plakophilin-2 c.419C>T and risk of heart failure and arrhythmias in the general population.
Eur. J. Hum. Genet. 2016, 24: 732–738.

Cirino AL, Harris S, Lakdawala NK, Michels M, Olivotto I, Day SM, Abrams DJ, Charron P, Caleshu C, Semsarian C, Ingles J, Rakowski H, Judge DP, Ho CY.
Role of Genetic Testing in Inherited Cardiovascular Disease: A Review.
JAMA Cardiol. 2017 Oct 1;2(10):1153-1160.

Clatot J, Ziyadeh-Isleem A, Maugenre S, Denjoy I, Liu H, Dilanian G, Hatem SN, Deschênes I, Coulombe A, Guicheney P, Neyroud N.
Dominant-negative effect of SCN5A N-terminal mutations through the interaction of Na(v)1.5 α-subunits.
Cardiovasc Res. 2012 Oct 1;96(1):53-63.

Corbin EA, Vite A, Peyster EG, Bhoopalam M, Brandimarto J, Wang X, Bennett AI, Clark AT, Cheng X, Turner KT, Musunuru K, Margulies KB.
ACS Appl Mater Interfaces. 2019 Jun 12;11(23):20603-20614.

Esslinger, U., Garnier, S., Korniat, A., Proust, C., Kararigas, G., Müller-Nurasyid, M., Empana, J.-P., Morley, M.P., Perret, C., Stark, K., Bick, A.G., Prasad, S.K., Kriebel, J., Li, J., Tiret, L., Strauch, K., O'Regan, D.P., Marguiles, K.B., Seidman, J.G., Boutouyrie, P., Lacolley, P., Jouven, X., Hengstenberg, C., Komajda, M., Hakonarson, H., Isnard, R., Arbustini, E., Grallert, H., Cook, S.A., Seidman, C.E., Regitz-Zagrosek, V., Cappola, T.P., Charron, P., Cambien, F., Villard, E.
Exome-wide association study reveals novel susceptibility genes to sporadic dilated cardiomyopathy.
PloS One 2017 Mar 15;12(3).

Fedida J, Fressart V, Charron P, Surget E, Hery T, Richard P, Donal E, Keren B, Duthoit G, Hidden-Lucet F, Villard E, Gandjbakhch E.
Contribution of exome sequencing for genetic diagnostic in arrhythmogenic right ventricular cardiomyopathy/dysplasia.
PLoS One. 2017 Aug 2;12(8).

Fressart V, Duthoit G, Donal E, Probst V, Deharo JC, Chevalier P, Klug D, Dubourg O, Delacretaz E, Cosnay P, Scanu P, Extramiana F, Keller D, Hidden-Lucet F, Simon F, Bessirard V, Roux-Buisson N, Hebert JL, Azarine A, Casset-Senon D, Rouzet F, Lecarpentier Y, Fontaine G, Coirault C, Frank R, Hainque B, Charron P.
Desmosomal gene analysis in arrhythmogenic right ventricular dysplasia/cardiomyopathy: spectrum of mutations and clinical impact in practice.
Europace. 2010 Jun;12(6):861-8.

Fujii Y, Itoh H, Ohno S, Murayama T, Kurebayashi N, Aoki H, Blancard M, Nakagawa Y, Yamamoto S, Matsui Y, Ichikawa M, Sonoda K, Ozawa T, Ohkubo K, Watanabe I, Guicheney P, Horie M.
A type 2 ryanodine receptor variant associated with

reduced Ca(2+) release and short-coupled torsades de pointes ventricular arrhythmia.
Heart Rhythm. 2017 Jan;14(1):98-107.

Gandjbakhch E, Redheuil A, Pousset F, Charron P, Frank R.
Clinical *Diagnosis, Imaging, and Genetics of Arrhythmogenic Right Ventricular Cardiomyopathy/ Dysplasia:* JACC State-of-the-Art Review.
J Am Coll Cardiol. 2018 Aug 14;72(7):784-804.

Garnier, S., Hengstenberg, C., Lamblin, N., Dubourg, O., De Groote, P., Fauchier, L., Trochu, J.-N., Arbustini, E., Esslinger, U., Barton, P.J., Meder, B., Katus, H., Frese, K., Komajda, M., Cook, S.A., Isnard, R., Tiret, L., Villard, E., Charron, P.
Involvement of BAG3 and HSPB7 loci in various etiologies of systolic heart failure: Results of a European collaboration assembling more than 2000 patients.
Int. J. Cardiol. 2015. 189, 105–107.

Hermida A, Fressart V, Hidden-Lucet F, Donal E, Probst V, Deharo JC, Chevalier P, Klug D, Mansencal N, Delacretaz E, Cosnay P, Scanu P, Extramiana F, Keller DI, Rouanet S, Charron P, Gandjbakhch E.
Eur J Heart Fail. 2019 Jun;21(6):792-800.

Itoh H, Berthet M, Fressart V, Denjoy I, Maugenre S, Klug D, Mizusawa Y, Makiyama T, Hofman N, Stallmeyer B, Zumhagen S, Shimizu W, Wilde AA, Schulze-Bahr E, Horie M, Tezenas du Montcel S, Guicheney P.
Asymmetry of parental origin in long QT syndrome: preferential maternal transmission of KCNQ1 variants linked to channel dysfunction.
Eur J Hum Genet. 2016 Aug;24(8):1160-6.

Kumar S, Baldinger SH, Gandjbakhch E, Maury P, Sellal JM, Androulakis AF, Waintraub X, Charron P, Rollin A, Richard P, Stevenson WG, Macintyre CJ, Ho CY, Thompson T, Vohra JK, Kalman JM, Zeppenfeld K, Sacher F, Tedrow UB, Lakdawala NK.
Long-Term Arrhythmic and Nonarrhythmic Outcomes of Lamin A/C Mutation Carriers.
J Am CollCardiol. 2016 Nov 29;68(21):2299-2307.

Pulcrano-Nicolas AS, Proust C, Clarençon F, Jacquens A, Perret C, Roux M, Shotar E, Thibord F, Puybasset L, Garnier S, Degos V, Trégouët DA.
Whole-Blood miRNA Sequencing Profiling for Vasospasm in Patients With Aneurysmal Subarachnoid Hemorrhage.
Stroke. 2018 Sep;49(9):2220-2223.

Richard P, Ader F, Roux M, Donal E, Eicher JC, Aoutil N, Huttin O, Selton-Suty C, Coisne D, Jondeau G, Damy T, Mansencal N, Casalta AC, Michel N, Haentjens J, Faivre L, Lavoute C, Nguyen K, Tregouët DA, Habib G, Charron P.
Targeted panel sequencing in adult patients with left ventricular non-compaction reveals a large genetic heterogeneity.
Clin Genet. 2018

Roux-Buisson N, Gandjbakhch E, Donal E, Probst V, Deharo JC, Chevalier P, Klug D, Mansencal N, Delacretaz E, Cosnay P, Scanu P, Extramiana F, Keller D, Hidden-Lucet F, Trapani J, Fouret P, Frank R, Fressart V, Fauré J, Lunardi J, Charron P.
Prevalence and significance of rare RYR2 variants in arrhythmogenic right ventricular cardiomyopathy/ dysplasia: Results of a systematic screening.
Heart Rhythm. 2014;11(11):1999-2009.

Salem JE, Germain M, Hulot JS, Voiriot P, Lebourgeois B, Waldura J, Tregouet DA, Charbit B, Funck-Brentano C.
GENomE wide analysis of sotalol-induced IKr inhibition during ventricular REPOLarization, «GENEREPOL study»: Lack of common variants with large effect sizes.
PLoS One. 2017 Aug 11;12(8).

Salem JE, Dureau P, Bachelot A, Germain M, Voiriot P, Lebourgeois B, Trégouët DA, Hulot JS, Funck-Brentano C.
Association of Oral Contraceptives With Drug-Induced QT Interval Prolongation in Healthy Nonmenopausal Women.
JAMA Cardiol. 2018 Sep 1;3(9):877-882.

Salem JE, Waintraub X, Courtillot C, Shaffer CM, Gandjbakhch E, Maupain C, Moslehi JJ, Badilini F, Haroche J, Gougis P, Fressart V, Glazer AM, Hidden-Lucet F, Touraine P, Lebrun-Vignes B, Roden DM, Bachelot A, Funck-Brentano C.
Hypogonadism as a Reversible Cause of Torsades de Pointes in Men.
Circulation. 2018 Jul 3;138(1):110-113.

Salem JE, Alexandre J, Bachelot A, Funck-Brentano C.
Influence of steroid hormones on ventricularrepolarization.
PharmacolTher. 2016 Nov;167:38-47.

Sené T, Lidove O, Sebbah J, Darondel JM, Picard H, Aaron L, Fain O, Zenone T, Joly D, Charron P, Ziza JM.
Cardiac device implantation in Fabry disease: A retrospective monocentric study.
Medicine (Baltimore). 2016 Oct;95(40).

Stillitano F, Hansen J, Kong CW, Karakikes I, Funck-Brentano C, Geng L, Scott S, Reynier S, Wu M, Valogne Y, Desseaux C, Salem JE, Jeziorowska D, Zahr N, Li R, Iyengar R, Hajjar RJ, Hulot JS.
Modeling susceptibility to drug-induced long QT with a panel of subject-specific induced pluripotent stem cells.
Elife. 2017 Jan 30;6.

Thevenon J, Laurent G, Ader F, Laforêt P, Klug D, DuvaPentiah A, Gouya L, Maurage CA, Kacet S, Eicher JC, Albuisson J, Desnos M, Bieth E, Duboc D, Martin L, Réant P, Picard F, Bonithon-Kopp C, Gautier E, Binquet C, Thauvin-Robinet C, Faivre L, Bouvagnet P, Charron P, Richard P.
High prevalence of arrhythmic and myocardial complications in patients with cardiac glycogenosis due to PRKAG2 mutations.
Europace. 2017 Apr 1;19(4):651-659.

Thuillot M, Maupain C, Gandjbakhch E, Waintraub X, Hidden-Lucet F, Isnard R, Ader F, Rouanet S, Richard P, Charron P.
External validation of risk factors for malignant ventricular arrhythmias in lamin A/C mutation carriers.
Eur J Heart Fail. 2019.

Veselka J, Anavekar NS, Charron P.
Hypertrophic obstructive cardiomyopathy.
Lancet. 2017 Mar 25;389(10075):1253-1267.

Villard E, Perret C, Gary F, Proust C, Dilanian G, Hengstenberg C, Ruppert V, Arbustini E, Wichter T, Germain M, Dubourg O, Tavazzi L, Aumont MC, DeGroote P, Fauchier L, Trochu JN, Gibelin P, Aupetit JF, Stark K, Erdmann J, Hetzer R, Roberts AM, Barton PJ, Regitz-Zagrosek V; Cardiogenics Consortium, Aslam U, Duboscq-Bidot L, Meyborg M, Maisch B, Madeira H, Waldenström A, Galve E, Cleland JG, Dorent R, Roizes G, Zeller T, Blankenberg S, Goodall AH, Cook S, Tregouet DA, Tiret L, Isnard R, Komajda M, Charron P*, Cambien F*.
A genome-wide association study identifies two loci associated with heart failure due to dilated cardiomyopathy.
Eur Heart J. 2011 May;32(9):1065-76.
*equal last author.

Vite A, Gandjbakhch E, Prost C, Fressart V, Fouret P, Neyroud N, Gary F, Donal E, Varnous S, Fontaine G, Fornes P, Hidden-Lucet F, Komajda M, Charron P, Villard E.
Desmosomal cadherins are decreased in explanted arrhythmogenic right ventricular dysplasia/cardiomyopathy patient hearts.
PLoS One. 2013; 8 (9).

COLLABORATIONS

FUNDS

EUROPAN / INTERNATIONAL

- H2020 2018 - 2020
- UE / ANR ERA-CVD 2018 - 2021
- EU-FP7 2013 - 2018
- Leducq Foundation 2012 - 2017

NATIONAL

- ANR 2014 - 2018
- Fondation Cœur & Recherche 2018 - 2019
- PHRC 2018 - 2023
- FFC/SFC 2015 - 2018

PRIVATE FOUNDATIONS

- Fondation maladies rares 2016 - 2018
- IHU-ICAN grants 2016 - 2020
- Fondation pour la Recherche Médicale 2018 - 2021
- Ligue contre la Cardiamyopathie 2014 - 2018
- Charty grant PROMEX 2017 - 2019

INDUSTRY

- SANOFI 2015 - 2018
- SHIRE 2014 - 2016

KEYWORDS

Genomics, heart, cardiomyopathies, IPS-derived cardiomyocytes, cardiac repolarization, sudden cardiac death, heart failure, precision medicine.

Team 2

ATHEROTHROMBOSIS AND APPLIED PHARMACOLOGY

THE TEAM

Jean-Philippe Collet

TEAM LEADER

Jean-Philippe COLLET, *MD, PhD, PU-PH, SU*

INVESTIGATORS

Gilles MONTALESCOT, *MD, PhD, PU-PH, SU*
Johanne SILVAIN, *MD, PhD, PU-PH, SU*
Ariel COHEN, *MD, PhD, PU-PH, SU*
Claude LEFEUVRE, *MD, PhD, PU-PH, SU*
Pascal LEPRINCE, *MD, PhD, PU-PH, SU*
Nadib HAMMOUDI, *MD, PhD, PU-PH, SU*
Guillaume LEBRETON, *MD, PhD, MCU-PH, SU*
Pierre DEMONDION, *MD, PhD, MCU-PH, SU*
Corinne FRERE, *MD, PhD, MCU-PH, SU*
Monique DAVID-DUFILHO, *PhD, CR, CNRS*
Michel ZEITOUNI, *PhD, MCU-PH, SU*

MEDICAL DOCTORS

Olivier BARTHELEMY, *MD, PH AP-HP*
Mathieu KERNEIS, *MD, PH, AP-HP*
Stéphane EDHERY, *MD, PH, AP-HP*
Laurie SOULAT-DUFOUR, *MD,PhD PH AP-HP*

TECHNICAL ASSISTANT

Delphine BRUGIER, *IR Action cœur*
Rabah JELLOUL, *AT Inserm*

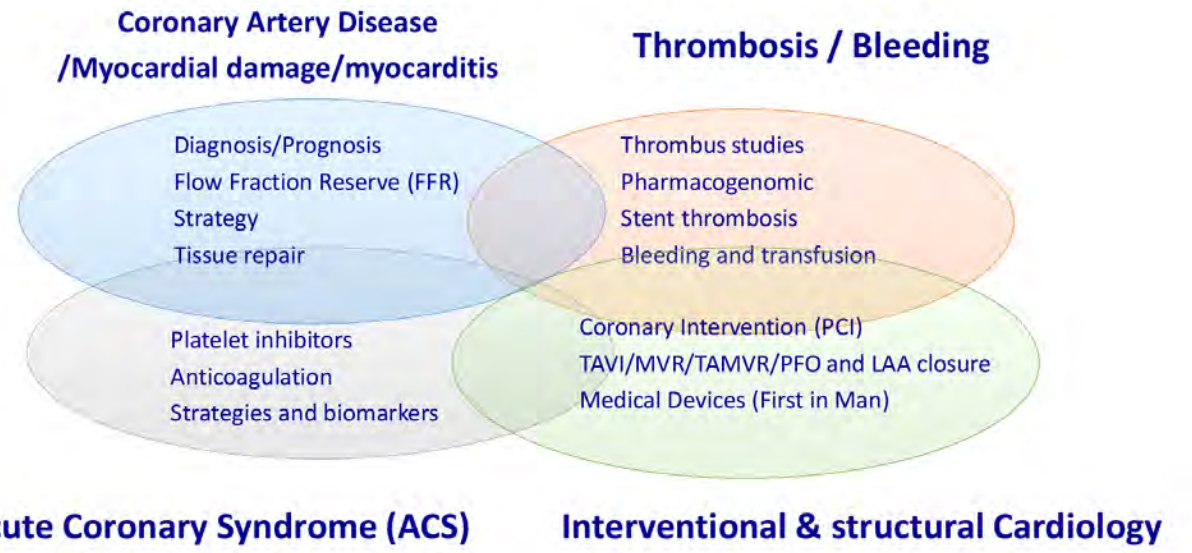
PHD STUDENTS

Paul GUEDENEY, *CCA*

>

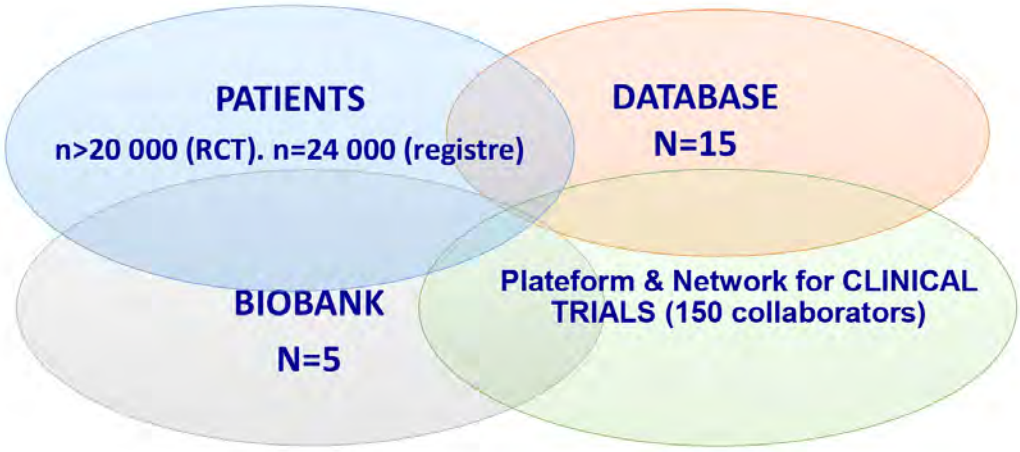
OBJECTIVES

THEMES



Our main goal is to improve knowledge in cardiovascular medicine from treatment strategies to education for primary prevention mainly in the field of atherothrombosis. Expanding of the group led to new areas of investigation including cardiovascular epidemiology, education technological innovations. Our cardiovascular research is broad going from in vitro experimental models to randomized clinical trials. It has always been focused on the same objectives, but projects have been diversified. The permanent interaction between clinicians and scientists within the same location is the major strength of the group. This unique set-up allows the attraction of fresh minds who volunteer for the challenge of clinical research. The development of new core lab facilities and our gained expertise in the field of clinical research via the ACTION study group are the key steps for a promising near future and facilitated interaction with basic science teams within UMRS 1166.

ORGANISATION AND TOOLS



MAIN AREAS OF EXPERTISE

- New models for experimental thrombosis
- Demonstration of the prognostic role of biomarkers
- Comparative evaluation of antithrombotic therapies
- Reassessment of antithrombotic drug regimens
- PK and PD models for drug evaluation
- Phase 1 study for oral antithrombotic treatment
- Use of metanalysis techniques
- Clinical and biological registries in atherothrombosis
- Core laboratory for angiography and biology
- Student tuition (Masters and PhD)(n=20).
- Randomized trials (www.action-coeur.org).

>

RESEARCH PROJECTS

CLINICAL AND SCIENTIFIC CONTEXT OF THE RESEARCH PROJECT

Atherothrombotic diseases are the leading cause of cardiovascular morbidity and mortality in developed countries, accounting for 54% of all deaths ahead of all cancer. One major breakthrough in this field came from the better understanding of thrombus formation including platelet activation and platelet aggregation intertwined with thrombin generation and fibrin clot propagation, all these pathways being temporally and spatially integrated. For instance, thanks to recent advances in intravital microscopy for real-time thrombus imaging and to new insights in the understanding of thrombus mechanical properties derived from both experimental model and ex vivo by electron microscopy, thrombogenesis is considered as a fast-acting process with a time window for each type of antithrombotic regimen (Silvain and al. JACC 2010). This has led to the concept of personalized medicine based on patient's antithrombotic treatment response according to phenotypes.

The discovery of the heterogeneous response to platelet antagonists among individuals led to the development of more potent antiplatelet drugs, further supportive of the concept and the need for personalized medicine. We described the detrimental effect of the CYP2C19*2 polymorphism carriage in clopidogrel treated patients who survived a stent thrombosis and the potential benefit of treatment escalation with prasugrel (Collet and al. Lancet 2009, Pena and al Circulation 2010). We launched then two large prospective studies to test the hypothesis of individualized oral antiplatelet agents based on platelet function testing in the setting of percutaneous coronary intervention -ARCTIC (Collet and al. NEJM 2012) and ANTARCTIC studies (Cayla and al. Lancet 2016). Furthermore, more than 10,000 patients were randomized in clinical studies led by our group (www.action-coeur.org). These studies included anticoagulation monitoring in the setting of PCI (ATOLL, Montalescot and al., Lancet 2011), pre-treatment effect with oral P2Y12 inhibitors in non-ST elevation myocardial infarction (ACCOAST Montalescot and al., NEJM 2013) and primary PCI for ST-elevation myocardial infarction (ATLANTIC study Montalescot and al., NEJM 2014). All these studies led to modifications of the ESC guidelines.

Personalized medicine for cardiovascular diseases is just starting nowadays. The next step is to integrate data generated by the "omic" approaches in comprehensive schemes that can be used in clinic to define therapeutic strategies for individual patient suffering from cardiovascular diseases. Progress in imaging of cardiovascular system will be determinant to elucidate the pathophysiological state of the disease process such as fibrosis of the myocardium. Finally, the development of medical devices opens new perspective for the tailoring of treatment of cardiovascular diseases.

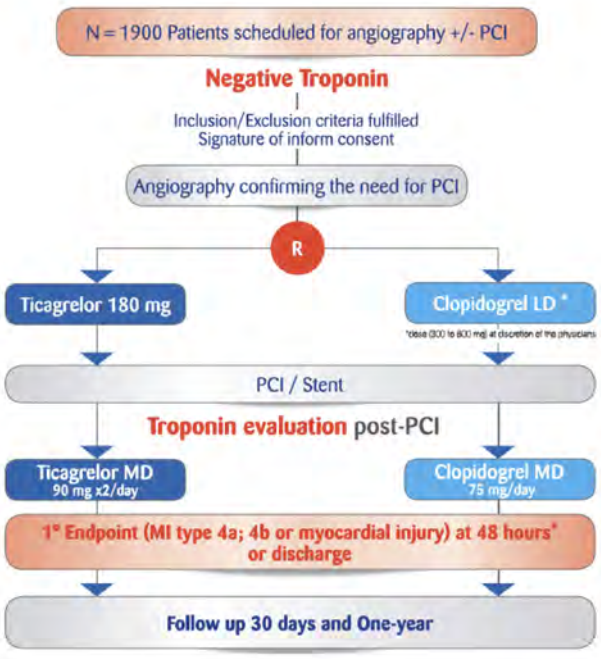
RESEARCH AXES

Our cardiovascular research is broad from in vitro experimental models to randomized clinical trials, all driven by the same goal: improve knowledge in cardiovascular medicine, from treatment strategies to education for primary prevention mainly in the field of atherothrombosis. Our main strength is the permanent interaction between clinicians and scientists at the same location.

CORONARY ARTERY DISEASE

Project 1: Escalation of P2Y12 inhibition in elective percutaneous coronary intervention (ALPHEUS study) and de-escalation of secondary prevention therapy following myocardial infarction (ABYSS study)

The new P2Y12 inhibitors prasugrel and ticagrelor have shown promising results and are recommended as first line treatments for acute coronary syndrome ACS (ESC Guidelines: Class 1 LOE B). These two drugs showed superiority over clopidogrel in ACS patients undergoing percutaneous coronary intervention (PCI), by the dramatic diminution of stent thrombosis, the reduction in death or Myocardial Infarction (MI) as well as the reduction in death in a meta-analysis. The field of elective PCI (stable patients) has not been studied with these 2 new drugs and clopidogrel remains the standard of care. However, off-label use of prasugrel and ticagrelor is increasing in patients undergoing high risk elective PCI (left main, diabetics, multiple stenting, high risk of stent thrombosis, no clopidogrel pretreatment...) but is not supported by scientific evidence. More than half of PCI patients undergo elective stenting for proven ischemia and/or stable angina, a relatively safe procedure with the use of the latest generation of stents. However complications remain either frequent when considering PCI-related myonecrosis/myocardial injury that have been linked to the prognosis of patients or rare but serious when considering stent thrombosis, Q wave MI or stroke, leaving room for improvement with these two newest drugs (Zeitouni M Eur Heart Journal 2018). We are currently performing a multicenter international study in stable patients undergoing elective PCI with a randomization between clopidogrel and ticagrelor. We are testing the superiority of the new P2Y12 inhibitor over clopidogrel in elective PCI on the primary ischemic endpoint (peri-procedural MI and myocardial injury) without significant excess bleeding (BARC definition).



The new P2Y12 inhibitors prasugrel (Efient®-Effient®) and ticagrelor (Brilique®-Brilinta®) have shown promising results in the respective TRITON and PLATO trials making of prasugrel and ticagrelor recommended first line treatments for acute coronary syndrome ACS (ESC Guidelines: Class 1 LOE B). These two drugs showed superiority over clopidogrel in ACS patients undergoing percutaneous coronary intervention (PCI), by the dramatic diminution of stent thrombosis, the reduction in death or Myocardial Infarction (MI) as well as the reduction in death in a meta-analysis.

The field of elective PCI (stable patients) has not been studied with these 2 new drugs and clopidogrel remains the standard of care. However, off-label use of prasugrel and ticagrelor is increasing in patients undergoing high risk elective PCI (left main, diabetics, multiple stenting, high risk of stent thrombosis, no clopidogrel pretreatment...) but is not supported by scientific evidence. More than half of PCI patients undergo elective stenting for proven ischemia and/or stable angina, a relatively safe procedure with the use of the latest generation of stents. However complications remain either frequent when considering PCI-related myonecrosis/myocardial injury that have been linked to the prognosis of patients or rare but serious when considering stent thrombosis, Q wave MI or stroke, leaving room for improvement with these two newest drugs.

We propose to perform a multicenter international study in stable patients undergoing elective PCI with a randomization between clopidogrel and ticagrelor. We hypothesize that this study will show superiority of the new P2Y12 inhibitor over clopidogrel in elective PCI on the primary ischemic endpoint (peri-procedural MI and myocardial injury) without significant excess bleeding (BARC definition).

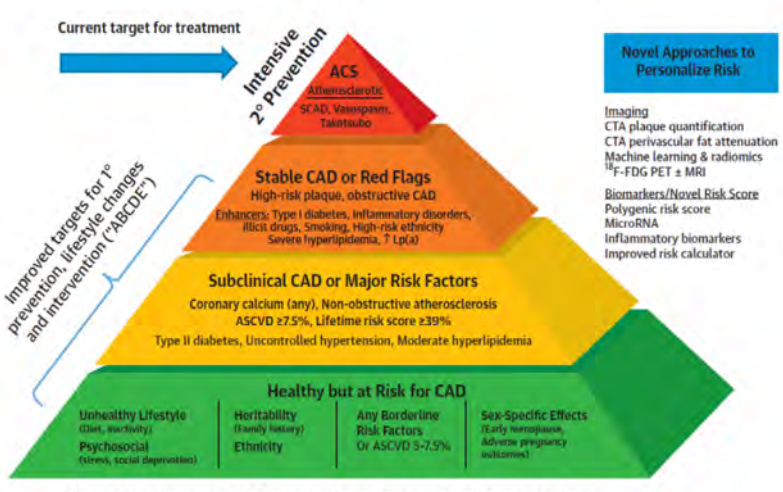
>

Project 2: Development of innovative POC diagnostic device "PLAT'IN" for platelet function assessment, including a first clinical validation step of a prototype

This project follows our previous studies on the interest of individualized oral antiplatelet agents based on platelet function testing in the setting of PCI. We will examine the interest of a new portable medical microfluidics device that generates strain rate conditions mimicking the effects of pathological changes in blood vessel (PLAT'IN). This system is based on a new principle of whole blood impedance measurements developed by Monique Dufilho and Francine Rendu. Commercial devices assessing platelet function have shown poor interest in adapting oral antiplatelet agents based on platelet function testing in clinical trials -ARCTIC (Collet et al. NEJM 2012) and ANTARCTIC studies. These commercial devices use in-vitro anticoagulant-agonist combinations such as citrate and ADP that do not take into account important aspects of in-vivo platelet function. It was recently demonstrated that antiplatelet agents have not the same effects at high pathological shear rates as compared to normal physiologic shear rates. Our innovating device using well-defined shear rates without the addition of antiplatelet therapies offers a new opportunity to study platelet function in pathological flow conditions. We will first provide a proof of concept for the interest of the PLAT'IN device in a first clinical validation step of the prototype. We will secondly design a multicenter prospective clinical trial to investigate the ability of the PLAT'IN device to assess individual response to antiplatelet drugs in pathological flow conditions and to further predict the risk of thrombosis in acute coronary syndrome patients.

Project 3: Pathophysiology of premature coronary artery disease (The AFIJI cohort project)

Coronary artery disease in young adults carries a poor long-term prognosis. The AFIJI (Appraisal of risk Factors in young Ischemic patients Justifying aggressive Intervention) registry has been launched in 1996 with the following objectives: 1) to evaluate the rate of first recurrent major adverse cardiovascular event (MACE) and associated risk factors; 2) to determine the relationship between the initial lesion and the new lesions; and 3) to determine the rate of repeated recurrences. At initial presentation, the average age was 40 years. One third of these patients had a recurrent MACE, and of these, 36% had at least a second recurrence. Key study findings were as follows: 1) recurrence rates remained high, despite medical therapy; 2) recurrent events generally occurred from new coronary lesions, which confirms prior work showing that non-obstructive plaques are the vulnerable ones, more prone to rapid progression (5); and 3) clinical factors associated with recurrence were insufficient control of conventional risk factors (diabetes, hypertension, and smoking), multivessel disease, Asian or sub-Saharan African ethnicity, and inflammatory disease. Smoking was the strongest modifiable factor for recurrent MACE. In sum, this study helped shed light on factors associated with progression and opportunities for enhanced prevention (4) (Collet JP, Zeitouni M et al. JACC 2019). The next step is to individualized potential independent prediction markers including inflammation, lipids pathway and cardiovascular imaging (aortic strain). All these studies are underway to better phenotype these patients.

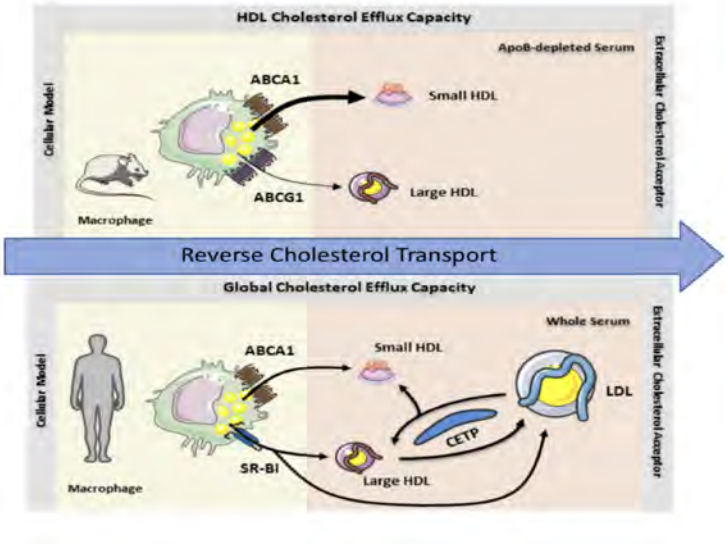


"Breaking the Cycle of Coronary Artery Disease in Young Adults"

CHOLESTEROL METABOLISM AND ACUTE MYOCARDIAL INFARCTION

Project 4: Cholesterol Efflux Capacity

Recent studies have established that cholesterol efflux capacity (CEC) better correlates with coronary artery diseases than high-density cholesterol (HDL-C) levels. The objective of the study was to evaluate whether CEC have a prognostic influence on mortality in high CV risk patients suffering from an acute myocardial infarction (AMI) and at high risk of occurrence of further cardiovascular events such as patients with STEMI, despite optimal medical therapy. Previous collaboration within UMRS 1166 allowed us to demonstrate that reduced CEC is associated with a decrease of both short term and long term survival of consecutive STEMI patients independently to either traditional cardiovascular risk factor including HDL-cholesterol levels or well established predictors of mortality in primary percutaneous coronary interventions (p PCI) population (Guerin M, Silvain J, JACC 2019).



Although low plasma HDL-C is firmly established as a cardiovascular (CV) risk factor, therapeutic HDL-C raising failed to reduce CV events in several large-scale clinical trials in patients treated with statins. Furthermore, data obtained using Mendelian randomisation do not support a causal relationship between HDL-C and CV risk. Taken together, those observations suggest that plasma HDL-C level measurement is a suboptimal indicator of the cardioprotective property of HDL particles. In an attempt to elucidate this controversy, Team 4 uncovered a major activity of HDL in postprandial metabolism and developed an assay in order to measure it. Team 4 in collaboration with team 2 are now evaluating the utility of this novel HDL functionality assay in the prediction of CV risk (morbidity and mortality) in a secondary prevention setting including patients with recent CV events (AMI, stroke, n $\geq$ 200, follow-up for $\geq$ 3 years).

INFLAMMATION AND CARDIOVASCULAR DISEASES

Inflammation had emerged as a key determinant of pathophysiology of several cardiovascular diseases. For instance, cardiac macrophages could have a protective or deleterious role in the transition from compensated cardiopathy to heart failure (see Team 3). Resident myocardial lymphocytes contribute to the fibrotic remodeling of the atrial subepicardial adipose tissue and the progression of the substrate of atrial fibrillation (Haemers and al. EHJ 2016). However, there are very few incentives for research on inflammatory disease and cardiovascular system in human. The heart institute of Pitié-Salpétrière is a leader in medical care of severe acute myocarditis. Myocarditis is an inflammatory disease of the myocardium and is diagnosed by biopsy using established immunohistochemical criteria. Characterization of this disease has been hampered by its heterogeneous clinical presentations and diverse aetiologies. It can be idiopathic, infectious or autoimmune and may lead to dilated cardiomyopathy.

Project 5: Myocarditis phenotyping and treatment intervention

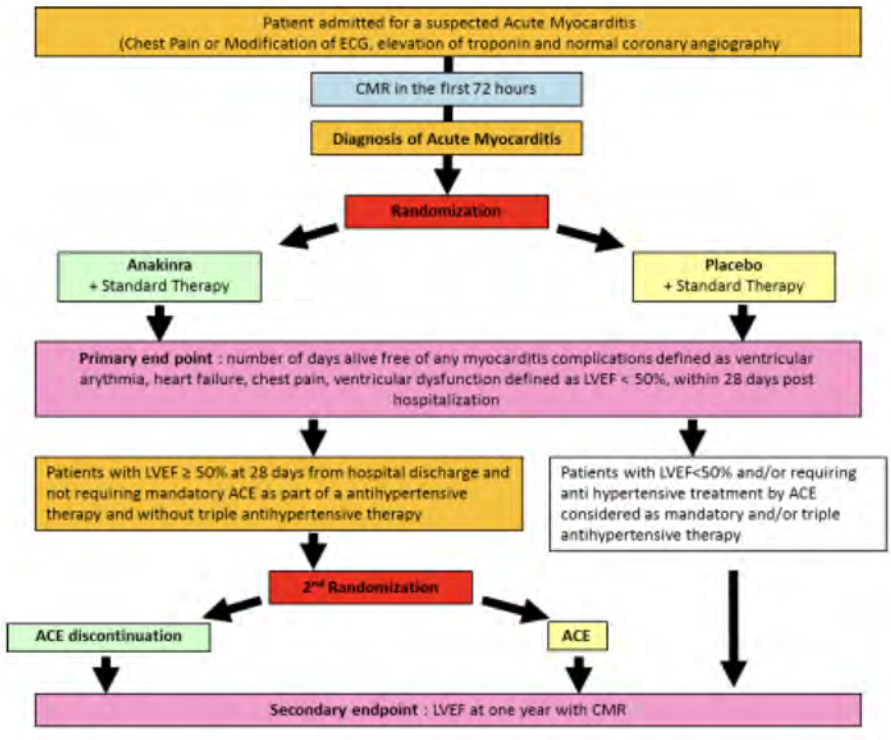
We have set-up an ongoing multicenter randomized trial on the therapeutic effect of IL1β antagonist (ARAMIS, M Kerneis). In this cohort of patients we will have unique access to bio resource including blood and myocardial samples. In collaboration with team-5, we will phenotype the immune cells by means of cytometric and metabolomics platforms. The goal is to characterize the type of immune cells recruited at the different stages of myocarditis and secondary to identify mechanisms underlying their recruitment and activation. This will contribute to design specific and target immunotherapy against myocarditis (Salem and Kerneis, N Engl J Med. 2019 Jun 13;380(24):2377-2379). Long-term follow-up and non-invasive cardiac assessment, as well deep systemic phenotyping, is needed to propose risk stratification and therapeutic options (immunosuppression, immunomodulation, antiviral therapy, etc.). A detailed Metabolomic analysis of the plasma of 120 Myocarditis patients will be performed using a untargeted approach able to detect and quantify more than 200 relevant metabolites in human plasma over 20 chemical classes. Our approach (Kayser and al, Int J Obes, 2017 ; Imene and al. Briefings in Bioinformatics, 2017) includes a database with more than 500 metabolites annotated representatives of the chemical compounds occurring in biofluids and cover the global map of metabolic pathways (Icanalytic). Additional phenotypic analysis of circulating immune cells by flow cytometry will be performed in order to monitor and characterized specific immune responses upon myocarditis (Icanalytic). These metabolomics and immune cells phenotyping approaches will be used to discover new biomarkers (diagnostic and prognostic biomarkers) and to give a molecular snapshot of patient response to therapies (anti-IL1β).

INNOVATIONS (2): first in man study with ANAKINRA for myocarditis

Aim: to assess the efficacy of ANAKINRA in Acute Myocarditis compared to placebo in addition to standard therapy.

There is no specific treatment of acute myocarditis, especially during the inflammatory period. Interleukin (IL) is specifically involved during this period and play a role in myocardial oedema. ANAKINRA, an IL-1β Blocker, is a new treatment that has never been evaluated in myocarditis. The benefit for the patient could be important with a reduction of heart failure and ventricular arrhythmias.

Primary Endpoint : number of days alive free of any myocarditis complications defined as ventricular arrhythmias, heart failure, chest pain, ventricular dysfunction defined as LVEF<50%, within 28 days post hospitalization



The ARAMIS Trial: « Anakinra versus placebo double blind Randomized controlled trial for the treatment of Acute MyocarditIS » (PHRC 2016)

CARDIOVASCULAR IMAGING

In vivo assessment of myocardial structure and function is a major challenge for personalized medicine of cardiovascular diseases. A better characterization of the structural and functional properties of the myocardium and vascular tree should allow an earlier detection of the disease and a better risk stratification of further events. Ultrasound imaging and MRI are major areas of investigation looking at myocardial wall deformation, an integrator of both contractile and histolgical properties of the myocardium (Huber AT and al. Radiology 2017; Wahbi K and al. Int J Cardiol. 2011). The following areas of investigation have been launched.

Project 6 : The cardiotoxicity of new angiogenic molecules developed for cancer treatment

Anthracyclines and molecular targeted agents have improved prognosis of patients undergoing chemotherapeutics for malignancy. However, the use of these therapies is limited because of risk of cardiac toxicity. Heart failure incidence rates associated with the commonly prescribed chemotherapy agents include 0.14–48 % for anthracyclines, 7-28% for high-dose cyclophosphamides and 8-12% for tyrosine kinase inhibitors. The severity of the cardiomyopathy can range from an asymptomatic left ventricular (LV) dysfunction to a severe congestive heart failure. Cardiomyopathy can be reversible or irreversible according to the type of chemotherapy, modality of administration and patient's characteristics. Therefore, the early detection of patients at risk to develop cardiac side effects and notably severe LV dysfunction is a major challenge. We will test the interest of left ventricular myocardial deformation assessing LV global longitudinal strain for the early detection of LV dysfunction in this clinical setting and using original acquisition approach and post-acquisition analysis developed in our core lab (Benyounes and al. Arch Cardiovasc Dis. 2015).

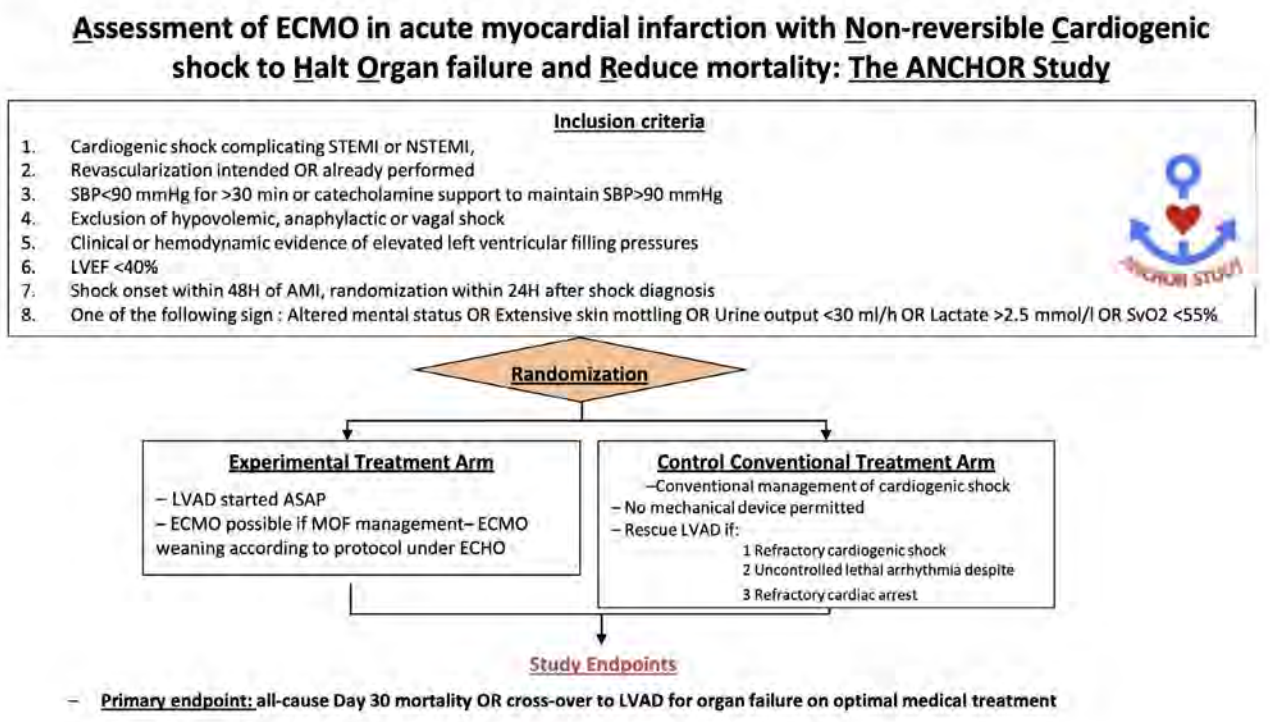
Project 7: Stroke of undetermined origin in the context of atrial fibrillation

Stroke is a major complication of cardiovascular diseases with two main causes: atherosclerosis and atrial fibrillation. Our group has done a seminal contribution in the ultrasound imaging of atheroma plaques and aorta thickness is the evolution of risk and origin of stoke (Amarenco P, Cohen A and al. N Engl J Med. 1994). Now we will study how to improve the detection of thombi formation in the atrium notably by studying the deformation of the let atrial appendage using speckle-tracing. We will confront the data obtained by ultrasound to new biological markers of thrombogenesis developed in the team notably platelet function using the PLAT'IN device.

Despite invasive treatment modalities such as early revascularization by percutaneous coronary intervention (PCI) and/or coronary artery bypass grafting (CABG), mortality of cardiogenic shock complicating acute myocardial infarction remains high with mortality rates ranging from 45% to 60%. Intraaortic balloon pumping (IABP) which was the most often used mechanical device for hemodynamic support in this situation did not significantly reduce 30-day and one-year mortality in patients with cardiogenic shock complicating acute myocardial infarction in a large randomized trial of almost 600 patients. In American and European guidelines, IABP use in cardiogenic shock is now only a class IIB and class IIC recommendation. Although recent case series of venoarterial extracorporeal membrane oxygenation (VA-ECMO) suggest markedly improved outcomes for refractory cardiogenic shock patients, no prospective randomized study has shown a survival benefit with VA-ECMO to date in this setting. Accordingly, the latest European guidelines afforded only a class IIB recommendation for left ventricle assist devices in patients with refractory cardiogenic shock. This underlines the need for an adequately powered randomized clinical trial to address the potential role of VA-ECMO in the treatment of cardiogenic shock complicating acute myocardial infarction, the most frequent cause of cardiogenic shock.

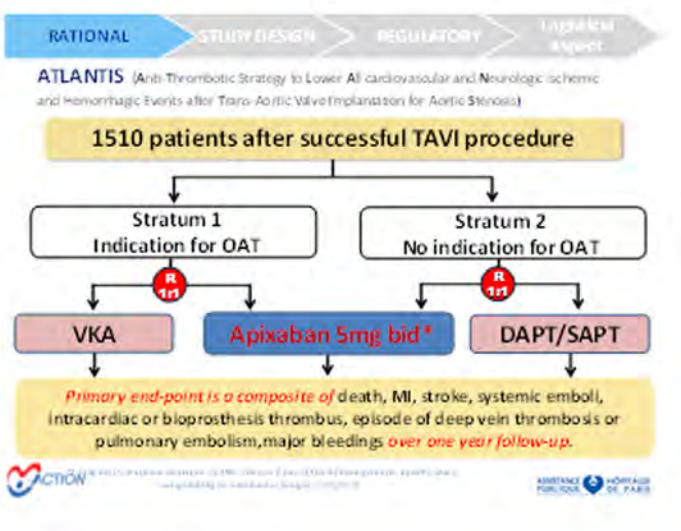
Project 8: The Anchor trial

The ANCHOR trial is designed to test the hypothesis that VA-ECMO support improves clinical outcome in comparison with optimal medical treatment with early revascularization in both groups. To determine if early VA-ECMO in conjunction with optimal medical treatment would improve clinical outcomes compared with optimal medical treatment alone in patients with acute myocardial infarction complicated by cardiogenic shock after early revascularization. The primary endpoint is all-cause Day 30 mortality OR cross-over to ECMO for organ failure on conventional arm strategy.



MEDICAL DEVICES

Percutaneous delivery of medical devices has become the first approach for treating coronary and structural disease including valvular heart disease. Understanding the interaction between circulating blood and implanted devices is one of the major challenges of modern cardiology. We are in the phase of embracing this scientific revolution with ongoing projects within the next 4 years.



Project 9: The ATLANTIS study

Guidelines on antithrombotic therapy after TAVI are scarce and no randomized evaluation has been performed to demonstrate what the optimal antithrombotic strategy is. The rates of major stroke and of major bleeding on DAPT, the standard of care in TAVI (Class IIb LOE C), are respectively as high as 3% and 10% within the first 30 days excluding the perioperative period. In addition, the rate of MACCE is estimated to be of 15% on DAPT. One third undergo coronary stent implantation prior to valve replacement and 1/3 display transient atrial fibrillation (AF) during hospital stay. Anticoagulation appears therefore to be underused in this high stroke risk population and has never been evaluated in post-TAVI procedures (Overtchouck P and Collet JP, 2019 JACC). The ATLANTIS trial is testing the hypothesis that apixaban is superior to SOC to prevent cardiovascular events in post-TAVI procedures. This study is coordinated by the ACTION study group (www.action-coeur.org). Ancillary imaging studies are looking at valve thrombosis and silent stroke.

SELECTED PUBLICATIONS

Collet JP, Zeitouni M, Procopi N, Hulot JS, Silvain J, Kerneis M, Thomas D, Lattuca B, Barthelemy O, Lavie-Badie Y, Esteve JB, Payot L, Brugier D, Lopes I, Diallo A, Vicaut E, Montalescot G; ACTION Study Group.
Long-Term Evolution of Premature Coronary Artery Disease.
J Am Coll Cardiol. 2019 Oct 15;74(15):1868-1878.

Salem JE, Allenbach Y, Vozy A, Brechot N, Johnson DB, Moslehi JJ, Kerneis M. Abatacept for Severe Immune Checkpoint Inhibitor-Associated Myocarditis. N Engl J Med. 2019 Jun 13;380(24):2377-2379
Overtchouk P, Guedeney P, Rouanet S, Verhoye JP, Lefevre T, Van Belle E, Eltchaninoff H, Gilard M, Leprince P, Iung B, Barthelemy O, Le Breton H, Souteyrand G, Vicaut E, Montalescot G, Collet JP.
Long-Term Mortality and Early Valve Dysfunction According to Anticoagulation Use: The FRANCE TAVI Registry.
J Am Coll Cardiol. 2019 Jan 8;73(1):13-21.

Guerin M, Silvain J, Gall J, Darabi M, Berthet M, Frisdal E, Hauguel-Moreau M, Zeitouni M, Kerneis M, Lattuca B, Brugier D, Collet JP, Lesnik P, Montalescot G.
Association of Serum Cholesterol Efflux Capacity With Mortality in Patients With ST-Segment Elevation Myocardial Infarction.
J Am Coll Cardiol. 2018 Dec 25;72(25):3259-326.

Montalescot G, van ‹t Hof AW, Lapostolle F, Silvain J, Lassen JF, Bolognese L, Cantor WJ, Cequier A, Chettibi M, Goodman SG, Hammett CJ, Huber K, Janzon M, Merkely B, Storey RF, Zeymer U, Stibbe O, Ecollan P, Heutz WM, Swahn E, Collet JP, Willems FF, Baradat C, Licour M, Tsatsaris A, Vicaut E, Hamm CW; ATLANTIC Investigators.
Prehospital ticagrelor in ST-segment elevation myocardial infarction.
N Engl J Med. 2014;371:1016-27.

Montalescot G, Bolognese L, Dudek D, Goldstein P, Hamm C, Tanguay JF, ten Berg JM, Miller DL, Costigan TM, Goedicke J, Silvain J, Angioli P, Legutko J, Niethammer M, Motovska Z, Jakubowski JA, Cayla G, Visconti LO, Vicaut E, Widimsky P, ACCOAST Investigators.
Pretreatment with prasugrel in non-ST-segment elevation acute coronary syndromes.
N Engl J Med. 2013 Sep 12;369(11):999-1010.

Montalescot G, Zeymer U, Silvain J, Boulanger B, Cohen C, Goldstein P, Ecollan P, Combes X, Huber K, Pollack C, Bénezet JF, Stibbe O, Filippi E, Teiger E, Cayla G, Elhadad S, Adnet F, Chouihed T, Gallula S, Greffet A, Aout M, Collet JP, Vicaut E. For the ATOLL *Investigators. Intravenous Enoxaparin or Unfractionated Heparin in Primary Percutaneous Coronary Intervention for ST-Elevation Myocardial Infarction: the International Randomized ATOLL Trial.*
Lancet. 2011 Aug 20;378(9792):693-703.

Cayla G, Cuisset T, Silvain J, Leclercq F, Manzo-Silberman S, Saint-Etienne C, Delarche N, Bellemain-Appaix A, Range G, El Mahmoud R, Carrié D, Belle L, Souteyrand G, Aubry P, Sabouret P, du Fretay XH, Beygui F, Bonnet JL, Lattuca B, Pouillot C, Varenne O, Boueri Z, Van Belle E, Henry P, Motreff P, Elhadad S, Salem JE, Abtan J, Rousseau H, Collet JP, Vicaut E, Montalescot G; ANTARCTIC investigators.
Platelet function monitoring to adjust antiplatelet therapy in elderly patients stented for an acute coronary syndrome (ANTARCTIC): an open-label, blinded-endpoint, randomised controlled superiority trial.
Lancet. 2016;388:2015-2022.

Beygui F, Cayla G, Roule V, Roubille F, Delarche N, Silvain J, Van Belle E, Belle L, Galinier M, Motreff P, Cornillet L, Collet JP, Furber A, Goldstein P, Ecollan P, Legallois D, Lebon A, Rousseau H, Machecourt J, Zannad F, Vicaut E, Montalescot G; ALBATROSS Investigators.
Early Aldosterone Blockade in Acute Myocardial Infarction: The ALBATROSS Randomized Clinical Trial.
J Am Coll Cardiol. 2016;67:1917-27.

Collet JP, Silvain J, Barthélémy O, Rangé G, Cayla G, Van Belle E, Cuisset T, Elhadad S, Schiele F, Lhoest N, Ohlmann P, Carrié D, Rousseau H, Aubry P, Monségu J, Sabouret P, O'Connor SA, Abtan J, Kerneis M, Saint-Etienne C, Beygui F, Vicaut E, Montalescot G, ARCTIC investigators.
Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-Interruption): a randomised trial.
Lancet. 2014;384:1577-85.

Collet JP, Cuisset T, Rangé G, Cayla G, Elhadad S, Pouillot C, Henry P, Motreff P, Carrié D, Boueri Z, Belle L, Van Belle E, Rousseau H, Aubry P, Monségu J, Sabouret P, O'Connor SA, Abtan J, Kerneis M, Saint-Etienne C, Barthélémy O, Beygui F, Silvain J, Vicaut E, Montalescot G; the ARCTIC Investigators.
Bedside Monitoring to Adjust Antiplatelet Therapy for Coronary Stenting.
N Engl J Med. 2012; 367(22):2100-9.

>

MAJOR FACTS 2012-2019

Personalized medicine: PFT to improve outcome after coronary intervention

- ARCTIC (Collet and al. NEJM 2012)
- ANTARCTIC (Cayla and al. Lancet 2016)

Pre-treatment in unstable coronary disease

- NSTEMI : ACCOAST (Montalescot and al. NEJM 2013)
- STEMI: ATLANTIC (Montalescot and al. NEJM 2014)

Duration of dual antiplatelet therapy with coronary angioplasty

- ARCTIC-INTERUPTION (Collet and al. Lancet 2014)

Phase 1 study with intravenous clopidogrel

- AMPHORE (Collet and al. Thromb Haemost 2016)

Transfusion and bleedings in CAD patients exposed to oral antiplatelet therapy

- TRANSFUSION-2 (Silvain and al. JACC 2014)
- APTITUDE (O'Connor and al. Circulation 2015)

Platelet Function test in special populations

- HIV: EVEREST (Haugel-Moreau EHJ 2017)
- Relay strategy (Kerneis M JACC Cardiovasc Interv. 2013)
- SENIOR Platelet (Silvain and al. JACC 2012)
- Exome sequencing of extreme clopidogrel response (Clin Pharmacol Ther. 2016)

Coronary artery disease

- Cholesterol efflux capacity (Guérin, Silvain and al. JACC 2019)
- Long-term outcome of premature CAD (Collet, Zeitouni and al. JACC 2019)

FUNDS

- European/international: H2020
- National: PHRC, Société Française de Cardiologie and Fédération Française de Cardiologie.
- Private foundations: FDD Action-coeur (www.action-fonds.org)
- Industry: SANOFI, ASTRA-ZENECA, MEDTRONIC, BOSTON, BMS/PFIZER.

KEYWORDS

Atherothrombosis, thrombosis, myocardial infarction, inflammation, hypercholesterolemia, percutaneous interventions, heart failure.

Team 3

MOLECULAR AND CELLULAR PLASTICITY IN CARDIOVASCULAR DISEASES

THE TEAM

TEAM LEADER

Elise BALSE, *PhD, MCU, SU*
Sophie NADAUD, *PhD, CR, Inserm*

INVESTIGATORS

Nicolas BADENCO, *MD, PH, AP-HP*
Sophie BESSE, *PhD, MCU, SU*
Serge CARREIRA, *MD, PH, AP-HP*
Alain COMBES, *MD, PhD, PU-PH, SU*
Mélanie EYRIES, *MD, AP-HP*
Yonathan FREUND, *MD, PhD, MCU-PH, SU*
Stéphane HATEM, *MD, PhD, PU-PH, SU*
Pierre HAUSFATER, *HDR PUPH SU*
Charles-Edouard LUYT, *MD, PhD, PU-PH, SU*
Bruno RIOU, *MD, PhD, PU-PH, SU*
Matthieu SCHMIDT, *MD, PhD, MCU-PH, SU*

Alain COULOMBE, *PhD, Volunteer*
Francine RENDU, *PhD, Emerita*
Florent SOUBRIER, *PhD, Emeritus*

TECHNICAL ASSISTANTS

Fabrice ATASSI, *AI, Inserm*
Gilles DILANIAN, *AI, Inserm*
Angèle FRISDAL, *IE SU*
Eva TRENQUIER RISSOAN, *AI SU*

POST-DOCTORAL FELLOWS

Basile GRAVEZ, *PhD, SU*
Nadine SUFFEE MOSBAH, *PhD, SU*

PHD STUDENTS

Chloé AZEVEDO
Camille BLANDIN
Brice GUENNEC
M. PINETON de CHAMBRUN
S. ROZENCWAJG, *Clinique Ambroise Paré*

OBJECTIVES

Cardiovascular diseases are often intricate diseases that share pathophysiological mechanisms. Remodeling processes are associated with complex rearrangement at the tissue and at the cellular levels. We aim at understanding the drivers of the molecular and cellular plasticity that characterize cardiovascular remodeling during atrial fibrillation (AF), heart failure (HF), senescence and pulmonary hypertension (PH).

Our projects focus on:

- The plasticity of cellular composition of cardiovascular tissues. We notably study the capacity of progenitor and stem cells to be recruited, to differentiate in various mesenchymal cell lineages and to contribute to atrial and vascular remodeling.

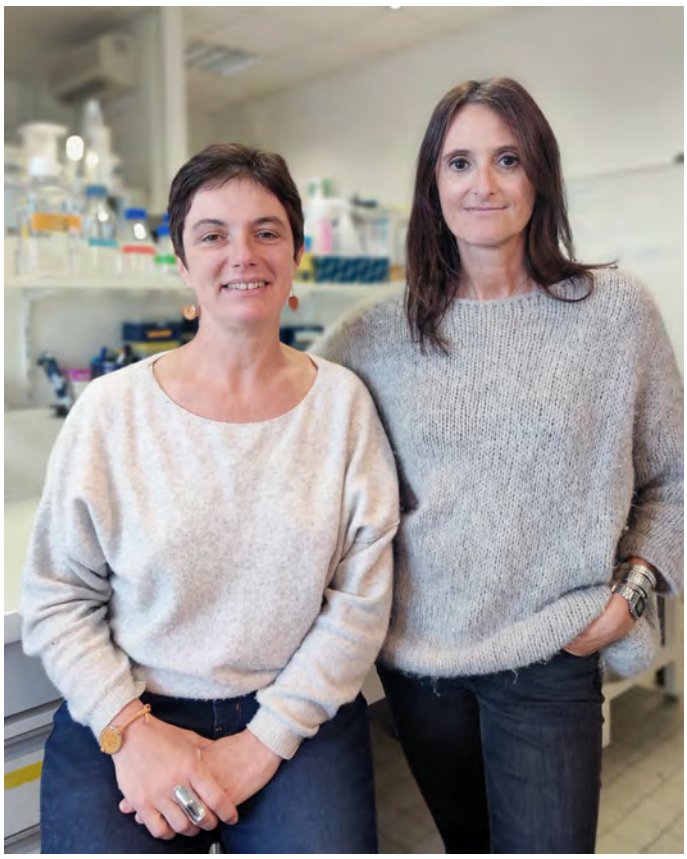
- The plasticity of macromolecular protein complexes regulating cardiac function and their role in pump dysfunction and arrhythmias. We focus on the regulation of ion channels trafficking and targeting in cardiomyocytes.

- The role of cellular metabolic shifts in regulating myocardial remodeling and atrial electrical properties.

- The role of immune and inflammatory cells during cardiovascular remodeling leading to HF. We study the mechanisms of macrophages protective role during early adaptive cardiac hypertrophy.

- The role of oxidative stress and inflammation during age-associated cardiovascular remodeling and transition to heart failure.

- The role of the GCN2 gene mutation in the development of pulmonary veno-occlusive disease, a specific form of pulmonary hypertension.



Sophie Nadaud and Elise Balse

Research projects

Atrial fibrillation and heart failure are two leading causes of worldwide mortality and morbidity in modern countries and their prevalence will continue to grow up in the next years with the ageing of population. Pulmonary hypertension is a rare and life-limiting cardiovascular disorder, characterized by an occlusive remodeling of the distal pulmonary vasculature that ultimately leads to right heart failure. Our team 3 is interested in deciphering the molecular and cellular players participating in the remodeling processes that lead to these pathologies.

>

RESEARCH PROJECTS

THEME 1 - MYOCYTE ORGANIZATION, ION CHANNEL SORTING AND TARGETING

E. BALSE

Scientific context and past contributions:
The functional expression of ion channels in the myocyte sarcolemma determines the shape and duration of the action potential, and therefore control the effective refractory period of the myocardium. The proper functional expression of ion channels can be disrupted at several levels such as transcriptional, translational and post-translational levels. Over the past years, we have contributed to better understand the dynamics of the surface expression of cardiac ion channels in cardiac myocytes (Balse et al. PNAS 2009, Balse et al., Physiol Rev 2012; Boycott et al., 2013; Eichel et al., Circ Res 2016). First, following our finding of reservoirs of KV channels beneath the sarcolemma quickly recycled ensuing cholesterol depletion (Balse et al., PNAS 2009; Balse et al., Physiol Review 2012), we showed that mechanical constraint triggers the exocytosis of Kv channels from this reservoir through the activation the integrin/PFAK mechanotransduction pathway. Recycling of KV1.5 channels becomes constitutive during atrial hemodynamic overload, supporting action potential shortening and arrhythmogenesis (Boycott et al., PNAS 2013) (Figure 1). In human biopsies from patients in AF, drastic modifications in the trafficking balance occurs together with alteration in microtubule polymerization state resulting in modest reduced endocytosis and increased recycling. Predominance of anterograde trafficking activity over retrograde trafficking consequently result in accumulation ok KV1.5 channels in the plasma membrane during atrial remodeling (BioRxive 805234).

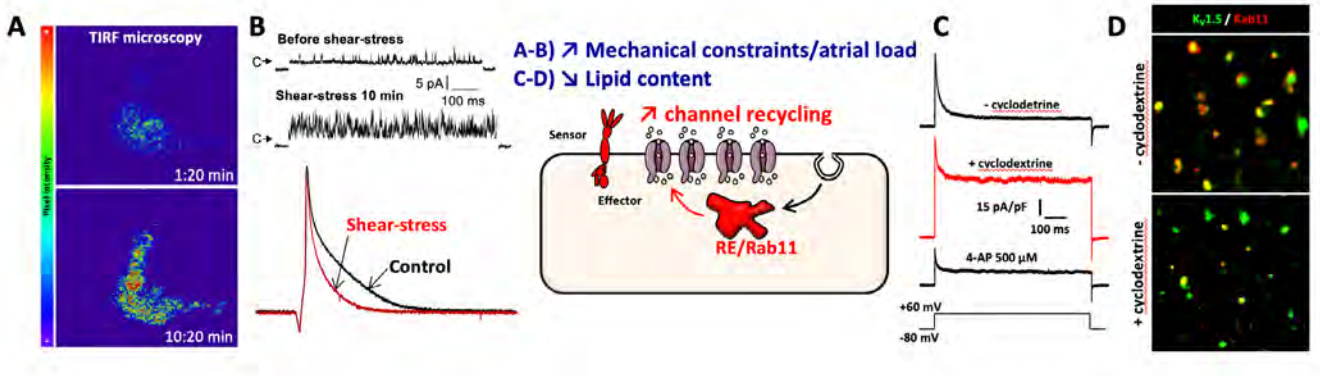


Figure 1. The recycling endosome is a major storage compartment of KV1.5 channels in atrial myocytes and ensure rapid delivery of channels upon changes in mechanical constraints.

Second, we previously characterized a new partner of the main cardiac sodium channel NaV1.5. Contrarily to other identified NaV1.5 partners, the MAGUK protein CASK negatively regulates lateral membrane pools of NaV1.5 by impeding anterograde trafficking of the channel. CASK is restricted to costameres, the focal adhesion of myocytes, and interact with dystrophin at the lateral membrane (Eichel et al. Circ Res 2016) (Figure 2). We have shown that both L27B and GUK domains are required for the negative regulatory effect of CASK on INa and NaV1.5 surface expression and that the HOOK domain is essential for interaction with the cell adhesion dystrophin-glycoprotein complex. Thus, due to its multi-modular structure, CASK could simultaneously interact with several targets in cardiomyocyte to potentially couple sodium channel trafficking to costameric cell adhesion in cardiomyocyte (BioRxive 813030).

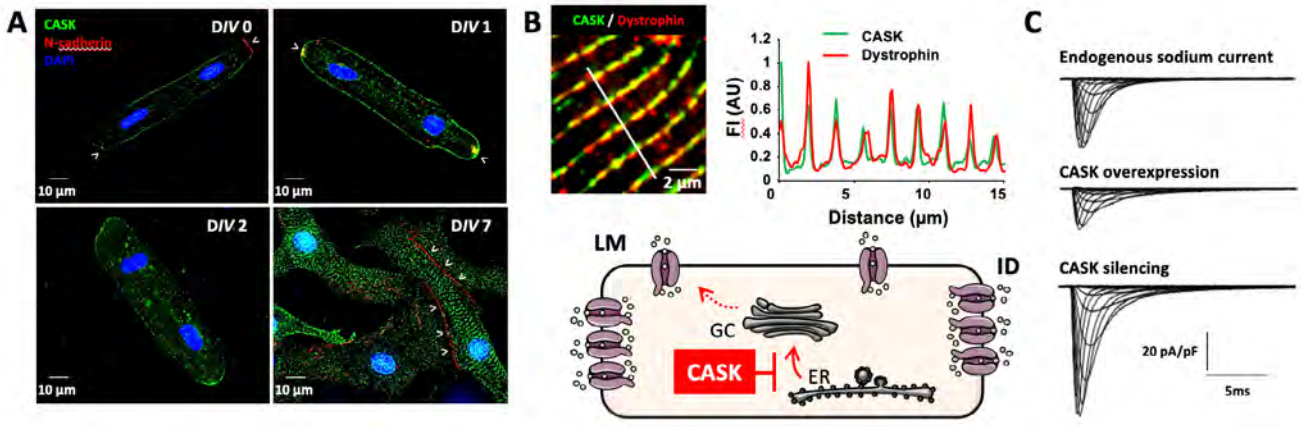


Figure 2. CASK impedes early anterograde trafficking of pools of channels targeted to the lateral membrane.

Scientific objectives:

These finding suggest a continuous interplay between membrane electrical properties, myocyte environment and 3-dimentional architecture of the myocardium. Overall, we will continue investigating the spatiotemporal organization of ion channels in cardiac myocytes, in relation with the microarchitecture of the tissue in normal and diseased conditions.

- Test the hypothesis of a sorting hub at early stages of trafficking, where interactions between NaV1.5 channels and regulatory partners orientate the final targeting of the channel in cardiac myocytes membrane subdomains.
- Investigate locally regulated exocytosis/endocytosis of ions channels regarding mechanotransduction sites in cardiac myocytes.
- Characterize the alterations of trafficking machinery in acquired cardiopathies and their role in the formation of the arrhythmogenic substrate.

Significance:

Beside better understanding of the general mechanisms of ion channel trafficking and targeting in cardiac myocytes, these studies should shed light on cardiac electrical plasticity in the context arrhythmias associated with myocardium structural remodelling as observed in most cardiopathies.

THEME 2

S. BESSE, B. RIOU

Our group is interested, since numerous years, in the mechanisms involved in cardiac aging and has contributed to identify structural changes of the myocardial tissue associated with electrical and mechanical remodeling in aged rodents (Fig. 1). The production of reactive oxygen species (ROS), not counterbalanced by anti-oxidant defenses which are deficient with age, has been implicated in this remodeling. ROS, which act as second messengers, modulate the activation/inactivation of various transcription factors such as NF-κB and FoxOs which in turn regulate many cellular pathways including inflammation, necrosis/apoptosis, ionic homeostasis, myocyte hypertrophy and remodeling of the extracellular matrix. Increasing evidence suggests that these transcription factors plays a central role in the transition from cardiac hypertrophy to heart failure at advanced age.

NF-κB activation induces chronic inflammation, which is a hallmark of heart failure and a predictor of overall prognosis, and can be obtained by two different routes: the canonical /classical and non-canonical pathways. Different studies proposed that damage/stress-mediated stimulation of NF-κB, likely contributes to aging mainly via the canonical pathway in different organism models but a cross-talk between these two identified pathways has been recently reported. FoxO3 plays an important role in protection of cells against oxidative stress and opposes NF-κB activation. In D. melanogaster FoxO3 overexpression suppresses age-associated diastolic dysfunction.

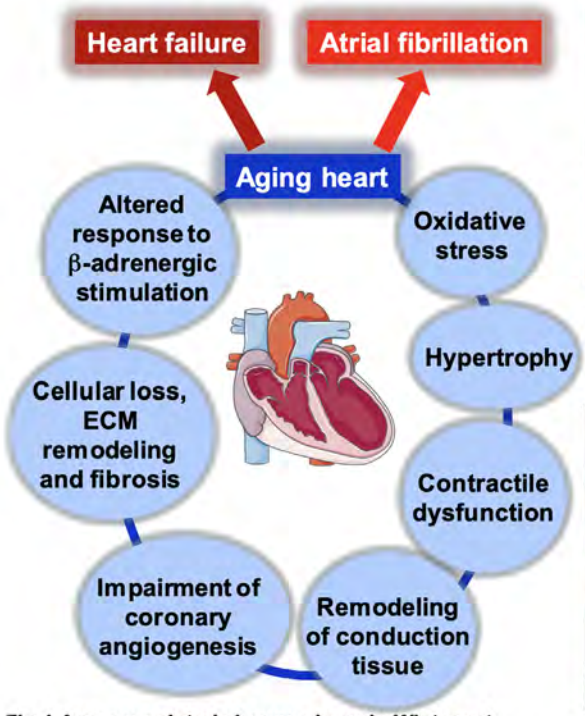
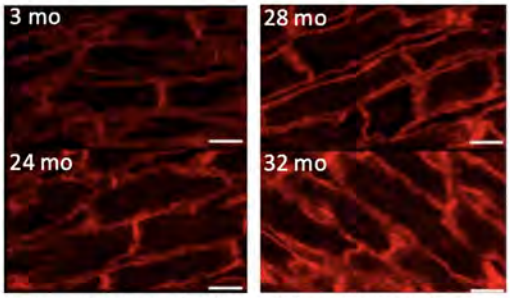
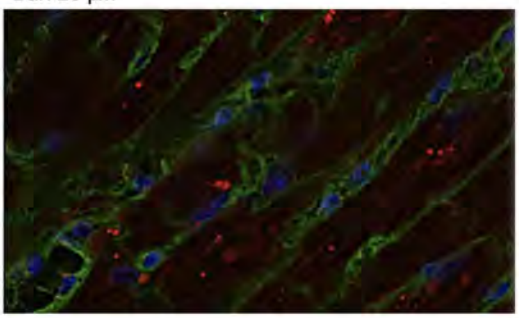


Fig.1 Age-associated changes in male Wistar rat
A synthesis from PMID: 28479388, 26084217, 25383567, 16413724, 21224495, 9166291, 7810723, 19034101). ECM: extracellular matrix



Immunolabeling of EMMPRIN, a MMP inducer in myocardium implicated in extracellular matrix remodeling from 3, 24, 28 and 32 mo male Wistar rats, showing that EMMPRIN increased with age. Bar: 20 µm



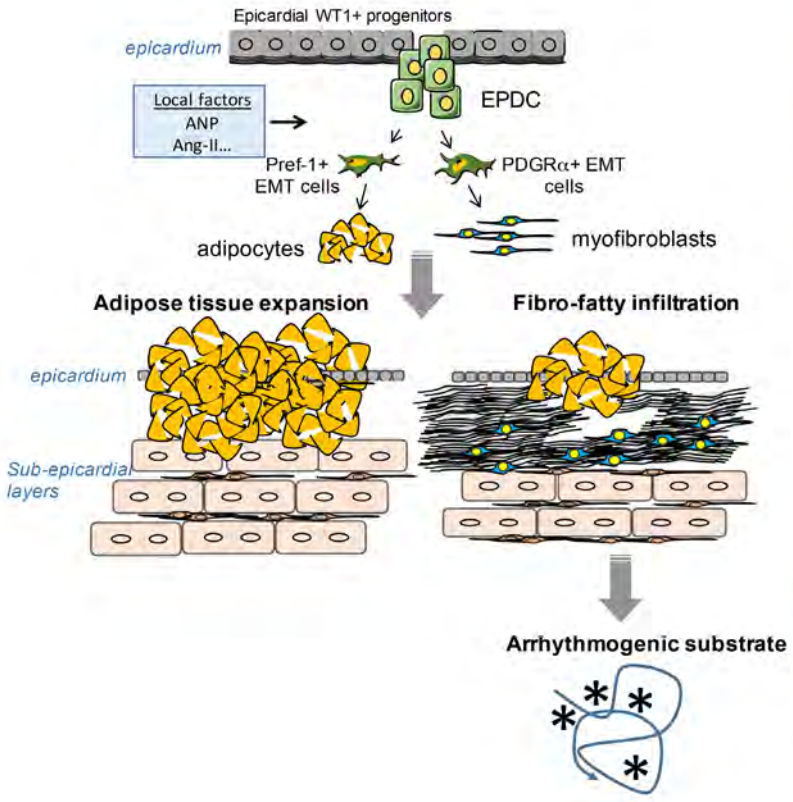
Immunolabeling of FoxO3 (red) in myocardium from 32 month old rat, showing age-associated cytoplasmic accumulation.

We are now investigating the regulatory pathways of oxidative stress and inflammation, especially alterations of FoxO and NF-κB signaling, in cardiac hypertrophy during aging in rodents to better understand the cellular and molecular mechanisms responsible for the transition to heart failure at advanced age. We are also studying these NF-κB and FoxO signaling pathways in human hearts which remains largely unexplored during aging.

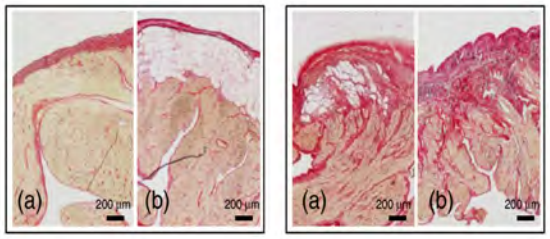
THEME 3

S. HATEM

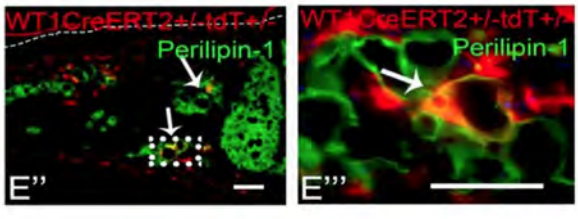
A number of clinical studies have established that adipose tissue accumulation at the atrial surface is a major risk factor for AF, especially during metabolic disorders such as obesity (Hatem JACC 2016). Our group was the first to demonstrate a causal link between epicardial adipose tissue and AF. We have identified adipokines secreted by the human atrial epicardial adipose tissue (Activin A) that can induce the fibrosis of neighboring atrial myocardium (Venteclef EHJ 2015). We described how fatty infiltrates become fibrotic in the atrial subepicardium, a remodeling process associated with persistent AF and mediated by an immune response involving T-lymphocytes (Haemers EHJ 2017). We found that adipocytes are derived from epicardial-based progenitor cells). The natriuretic peptide secreted by atrial myocytes in response to mechanic stress is a powerful adipogenic factor for the epicardial progenitors at low concentration (Suffee PNAS 2017). Recently we identified subpopulation of epicardial progenitors engaged toward adipocyte or fibroblast differentiation and the signaling pathways that govern such a switch (BioRxiv 589705). In collaboration with LIB teams (Biomedical imaging laboratory) and using in-house algorithms, we established that atrial wall strain correlates with the degree of atrial fibro-fatty infiltration which can be used as a biomarker of the AF substrate (Hubert Radiology 2018). We also identified high-field MRI sequences which enables analysis adipose tissue infiltrates of the myocardium (Bouazizi PLoS One 2019).



Epicardium is reactived early during the formation of the atrial cardiomyopathy and the substrate of atrial fibrillation. The recruitment of cells derived from epicardial progenitors and pre engaged in the distinct adipocyte or fibroblastic lineages can result in the arrhythmogenic fibro-fatty infiltration of atrial subepicardial layers.



Fibrotic remodelling (Sirius red staining) of the epicardium in human atrial samples. Non-fibrotic remodelled epicardium, without (A) or with (B) subepicardial adipose tissue and fibrotic remodelled epicardium with (C) or without (D) subepicardial adipose tissue.



Coimmunostaining for Perilipin-1 (adipogenic marker) and Tomato (marking cells derived from WT1+ epicardial cells) in atrial cells of mice fed a high fat diet. Arrows indicate epicardium-derived adipocytes coexpressing Tomato and Perilipin

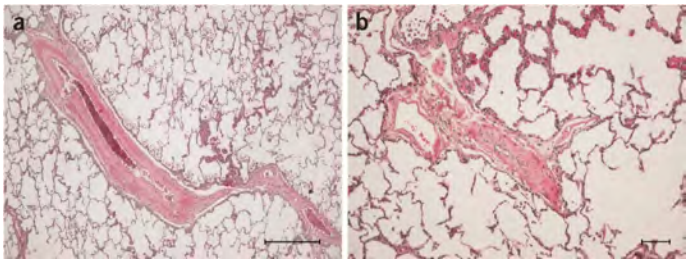
THEME 4

C. PAVOINE

Scientific context. Cardiac hypertrophy (CH) is initially a compensatory process to optimize cardiac pump function. However, CH is progressively associated with structural changes that become pathogenic, with cardiomyocyte death, induction of exacerbated inflammatory responses and interstitial fibrosis. These harmful changes ultimately lead to transition to heart failure (HF). Activation of the sympathetic nervous system plays a determinant role in the induction of early adaptive CH (EACH) and further progression to pathological remodeling. Cardiac remodeling is a complex inflammatory syndrome, and beneficial or detrimental role of inflammatory signaling during EACH is not fully understood. Growing evidence indicates that inflammatory responses emerging in EACH and HF are different, displaying divergent cytokine and chemokine profiling. The pro-inflammatory cytokine TNFα is upregulated in CH and HF. In the 1990's, the "cytokine hypothesis" argued for the detrimental contribution of an excessive production of TNFα to the pathogenesis of HF suggesting that TNFα neutralization would be beneficial. Surprisingly, large clinical trials failed to demonstrate a benefit of anti-TNFα strategies. There is now evidence that TNFα can also improve remodeling and hypertrophy and alleviate inflammation and fibrosis.

In addition to cardiomyocyte hypertrophy, cardiac hypertrophy (CH) is associated with determinant changes of non-myocyte cardiac cell types, including macrophages (Mφ). Cardiac Mφ influence tissue homeostasis, repair and regeneration. They modulate CH and HF, in particular through the regulation of pro- or anti-inflammatory paracrine signaling. However, the functions of cardiac Mφ are not fully understood especially in the context of cardiac hypertrophic remodeling in diseases from non-ischemic origin. Catherine Pavoine's group recently highlighted that cardiac inflammatory CD11b/c cells exert a protective role in hypertrophied cardiomyocyte by promoting TNFR 2 - and Orai3- dependent signaling (Keck M et al., Sci Rep 2019). Emergence of this novel protective paracrine role of CD11b/c cells during EACH, improves resistance of adult hypertrophied cardiomyocytes to oxidative stress and potentially limits evolution towards HF in response to β-adrenergic stimulation.

Objective. The group is now seeking to identify the origin and role of macrophages selectively amplified in EACH as compared to control and HF hearts in order to better define their protective mechanism of action. Prelimary results identify the crucial role of the CX3CL1/CX3CR1 axis (submitted to publication).
Aim1: Using flow cytometry, transcriptomic, lipidomic and secretomic approaches, the group will identify typical markers, genes, lipids, proteins and secreted chemokines characterizing EACH Mφ.
Aim2: the group will perform in vitro and in vivo experiments to elucidate the impact of these typical signals on cardiomyocyte hypertrophy and survival, and on EACH and HF transition.



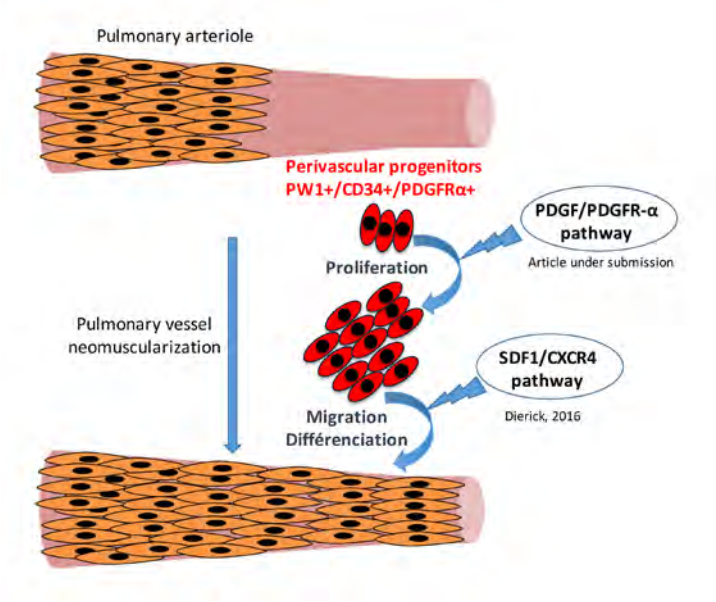
Protective role of macrophages via the CX3CL1/CX3CR1 axis in early adaptive cardiac hypertrophy remodeling. Chronic β-adrenergic stimulation elicits a CX3CL1/CX3CR1-dependent expansion of CD64+ CCR2- LY6C-MHCIIlow Macrophages. CX3CL1 increases the number and the proliferative activity of cardiac macrophages. CX3CL1 and TNF-α secreted by cardiac macrophages synergistically trigger cardiomyocyte hypertrophy. This early adaptative cardiac remodeling limits evolution towards heart failure.

THEME 5

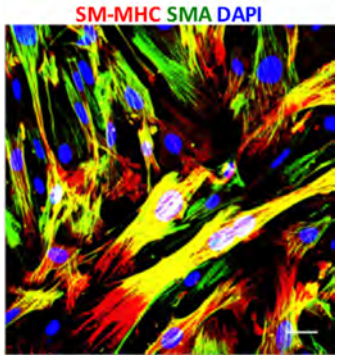
S. NADAUD

Our group is interested in the cellular and molecular factors involved in regulating vascular remodeling. We are in particular investigating the origin of new smooth muscle cells produced during pulmonary hypertension. This is a rare and devastating disease with no curative options, characterized by an occlusive remodeling of the distal pulmonary vasculature that ultimately leads to right heart failure. Non-muscularized vessels become muscularized and vessels media thickness is increased with in addition, neointima formation. Resident pulmonary progenitors participate in the pulmonary hypertension-associated vascular remodeling by generating new smooth muscle cells. We have identified resident CD34+/PW1+/PDGFRα+ progenitors involved in the early neomuscularization observed during chronic hypoxia (CH: a model for moderate pulmonary hypertension) (Dierick, Circ Res 2016). We have recently demonstrated that the proliferation of these progenitor cells is under the control of the PDGFRα pathway (article in preparation). In collaboration with C. Guignabert (INSERM U999), we have studied pulmonary NG2+ pericytes which are also vascular progenitor cells activated during pulmonary hypertension (article submitted). We develop lineage tracing models to follow the fate of these progenitor cells during pulmonary hypertension associated vascular remodeling. We use transgenic mouse models to induce or suppress PDGFRα activity in vivo following tamoxifen activation to evaluate the role of this pathway in the function of these progenitors and in CH-induced vascular remodeling.

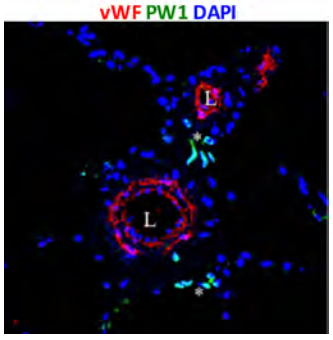
We are now investigating the role of metabolic alterations on pulmonary vascular progenitor cells recruitment. In addition, we are studying the role of the PDGFRα pathway and of the vascular progenitor cells in the systemic vascular remodeling during other cardiovascular disorders leading to vascular remodeling.



Pulmonary arterioles are mainly non muscularized and neomuscularization is a hallmark of pulmonary hypertension. Our data show that pulmonary vascular progenitor cells are recruited by PDGFRα signalling activation and differentiate into new smooth muscle cells following CXCR4 signalling.



Progenitor cells in culture differentiate into smooth muscle cells identified by SM-MHC (red) and α-SMA (green) expression



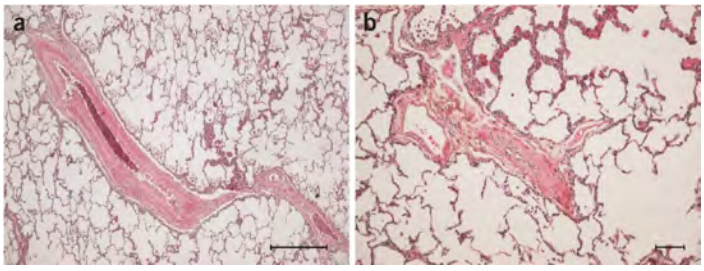
PW1+ Progenitor cells (green) are clustered around vessels (red) in control human lung

THEME 6

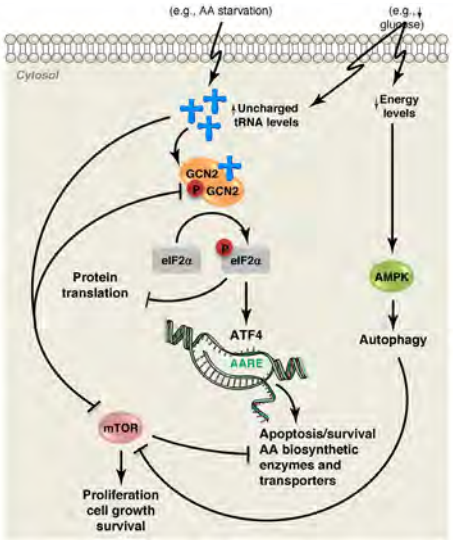
F. SOUBRIER

Florent Soubrier's group, in tight link with the clinical genetics laboratory of the campus hospital (Pitié-Salpêtrière hospital) has identified genes involved in the genetic predisposition to pulmonary arterial hypertension (PAH) and pulmonary veno-occlusive disease (PVOD). In 2019, this group has identified BMP10 as a new gene for heritable PAH (PMID: 30578383) and has identified two families presenting with heritable PAH and carrying mutations of the KDR gene encoding VEGFR2 (Eyries and al. in revision 2019). One objective of the group is to identify new predisposing genes and whole genome sequencing is the technique used in selected subjects.

The group is also investigating the cellular and molecular mechanisms underlying the occurrence of the heritable form of pulmonary veno-occlusive disease (PVOD) due to mutation of the EIF2AK4 gene that this group has identified in 2015 (PMID: 24292273). This gene encodes GCN2, a serine-threonine kinase which is one of the four EIF2α kinase and induces the integrated stress response in the cell in response to amino acid deprivation. GCN2 has important interactions with cellular physiological responses such as autophagy, inflammation and oxidative stress and with other signaling systems such as mTOR. The link between complete loss of GCN2 and PVOD is not elucidated and is the goal of intensive research. Three lines of rats carrying deletions of EIF2AK4 have been obtained through CrispR-CAS9 gene targeting and are used for deciphering, in vivo, the modes of initiation of the disease.



Pathology of heritable PVOD. (a) septal vein and (b) small vein showing intimal fibrosis and thickening of the vascular wall (from Eyries and al. PMID: 24292273).



Schematic view of the GCN2 induced activation of integrated stress response. Amino acid deprivation induces GCN2 dimerization and activation, hence inducing phosphorylation of the α subunit of EIF2 (EIF2a) which in turn inhibits protein translation and increases ATF4 by a translational mechanism. ATF4 is a transcription factor that has several transcriptional targets. During inflammation, there is an amino acid consumption by cell proliferation and that causes GCN2 activation. Figure from Santos-Ribeiro D (PMID: 29499378).

SELECTED PUBLICATIONS

Dario Melgari, Camille Barbier, Gilles Dilanian, Catherine Rücker-Martin, Nicolas Doisne, Alain Coulombe, Stéphane N. Hatem, Elise Balse
Microtubule polymerization state and clathrin-dependent internalization regulate dynamics of cardiac potassium channel
bioRxiv 805234.

Adeline Beuriot, Catherine A. Eichel, Gilles Dilanian, Florent Louault, Dario Melgari, Nicolas Doisne, Alain Coulombe, Stéphane N. Hatem, Elise Balse
Distinct CASK domains control cardiac sodium channel membrane expression and focal adhesion anchoring
bioRxiv 813030.

Boutry M, Pierga A, Matusiak R, Branchu J, Houllegatte M, Ibrahim Y, Balse E, El Hachimi KH, Brice A, Stevanin G, Darios F.
Loss of spatacsin impairs cholesterol trafficking and calcium homeostasis.
Commun Biol. 2019 Oct 17;2:380.

Keck M, Flamant M, Mougenot N, Favier S, Atassi F, Barbier C, Nadaud S, Lompré AM, Hulot JS, Pavoine C.
Cardiac inflammatory CD11b/c cells exert a protective role in hypertrophied cardiomyocyte by promoting TNFR2- and Orai3- dependent signaling.
Sci Rep. 2019;9(1):6047.

Ulrich A, Wharton J, Thayer TE, Swietlik EM, Assad TR, Desai AA, Gräf S, Harbaum L, Humbert M, Morrell NW, Nichols WC, Soubrier F, Southgate L, Trégouët DA, Trembath RC, Brittain EL, Wilkins MR, Prokopenko I, Rhodes CJ, NIHR BioResource – Rare Diseases Consortium; UK PAH Cohort Study Consortium; US PAH Biobank Consortium.
Mendelian randomisation analysis of red cell distribution width in pulmonary arterial hypertension.
Eur Respir J. 2019. Nov 19.

Chua W, Easter CL, Guasch E, Sitch A, Casadei B, Crijns HJGM, Haase D, Hatem S, Kääb S, Mont L, Schotten U, Sinner MF, Hemming K, Deeks JJ, Kirchhof P, Fabritz L.
Development and external validation of predictive models for prevalent and recurrent atrial fibrillation: a protocol for the analysis of the CATCH ME combined dataset.
BMC Cardiovasc Disord. 2019;19(1):120.

Eyries M, Montani D, Nadaud S, Girerd B, Levy M, Bourdin A, Trésorier R, Chaouat A, Cottin V, Sanfiorenzo C, Prevot G, Reynaud-Gaubert M, Dromer C, Houeijeh A, Nguyen K, Coulet F, Bonnet D, Humbert M, Soubrier F.
Widening the landscape of heritable pulmonary hypertension mutations in pediatric and adult cases.
Eur Respir J. 2019 Mar 14; 53(3).

Levy M, Del Cerro M-J, Nadaud S, Vadlamudi K, Colgazier E, Fineman J, Bonnet D, Adatia I.
Safety, Efficacy and Management of Subcutaneous Treprostinil Infusions in the Treatment of Severe Pediatric Pulmonary Hypertension.
Int J Cardiol. 2018 Aug 1; 264:153-157.

Bouazizi K, Rahhal A, Kusmia S, Evin M, Defrance C, Cluzel P, Berthet M, Atassi F, Leprince P, Lebreton G, Kachenoura N, Hatem SN, Redheuil A.
Differentiation and quantification of fibrosis, fat and fatty fibrosis in human left atrial myocardium using ex vivo MRI.
PLoS One. 2018 Oct 8; 13(10).

Sawaki D, Czibik G, Pini M, Ternacle J, Suffee N, Mercedes R, Marcelin G, Surenaud M, Marcos E, Gual P, Clément K, Hue S, Adnot S, Hatem SN, Tsuchimochi I, Yoshimitsu T, Hénégar C, Derumeaux G.
Visceral Adipose Tissue Drives Cardiac Aging Through Modulation of Fibroblast Senescence by Osteopontin Production.
Circulation. 2018 Aug 21; 138(8):809-822.

>

Huber AT, Lamy J, Rahhal A, Evin M, Atassi F, Defrance C, Lebreton G, Clément K, Berthet M, Isnard R, Leprince P, Cluzel P, Hatem SN, Kachenoura N, Redheuil A.
Cardiac MR Strain. A Noninvasive Biomarker of Fibrofatty Remodeling of the Left Atrial Myocardium.
Radiology. 2018 Jan; 286(1):83-92.

Balse E, Eichel C.
The Cardiac Sodium Channel and Its Protein Partners.
Handb Exp Pharmacol. 2018;246:73-99.

Zerah L, Dourthe L, Cohen-Bittan J, Verny M, Raux M, Mézière A, Khiami F, Tourette C, Neri C, Le Manach Y, Riou B, Vallet H, Boddaert J.
Retrospective Evaluation of a Restrictive Transfusion Strategy in Older Adults with Hip Fracture.
J Am Geriatr Soc. 2018 Jul; 66(6):1151-1157.

Le Dinh M, Carreira S, Obert J, Gayan-Ramirez G, Riou B, Beuvin M, Similowski T, Coirault C, Demoule A.
Prolonged mechanical ventilation worsens sepsis-induced diaphragmatic dysfunction in the rat.
PLoS One. 2018 Aug 1; 13(8).

Huber AT, Lamy J, Rahhal A, Evin M, Atassi F, Defrance C, Lebreton G, Clément K, Berthet M, Isnard R, Leprince P, Cluzel P, Hatem SN, Kachenoura N, Redheuil A.
Cardiac MR strain: a noninvasive biomarker of fibro-fatty remodeling of the left atrial myocardium.
Radiology. 2018 Jan; 286(1) 83-92.

Suffee N, Moore-Morris T, Farahmand P, Rücker-Martin C, Dilanian G, Fradet M, Sawaki D, Derumeaux G, LePrince P, Clément K, Dugail I, Puceat M, Hatem SN.
Atrial natriuretic peptide regulates adipose tissue accumulation in adult atria.
Proc Natl Acad Sci U S A. 2017 Jan31; 114 (5):E771-E780.

Balse E, Boycott HE.
Ion Channel Trafficking: Control of Ion Channel Density as a Target for Arrhythmias?
Front Physiol.2017 Oct 17;8:808.

Haemers P, Hamdi H, Guedj K, Suffee N, Farahmand P, Popovic N, Claus P, LePrince P, Nicoletti A, Jalife J, Wolke C, Lendeckel U, Jaïs P, Willems R, Hatem SN.
Atrial Fibrillation Is Associated with the Fibrotic Remodelling of Adipose Tissue in the Subepicardium of Human and Sheep Atria.
European Heart J 2017 Jan 1; 38 (1): 53–61.

Thompson E, Eldstrom J, Westhoff M, McAfee D, Balse E, Fedida D.
cAMP-Dependent Regulation of IKs Single Channel Kinetics,
J Gen Physiol. 2017 Aug 7;149(8):781-798.

Deloge E, Amour J, S Provenchère, B Rozec, B Scherrer, A Ouattara.
Aprotinin vs. Tranexamic Acid in Isolated Coronary Artery Bypass Surgery: A Multicentre Observational Study.
Eur J Anaesthesiol. 2017 May; 34 (5): 280–87.

Hulot JS, Salem JE, Redheuil A, Collet JP, Varnous S, Jourdain P, Logeart D, Gandjbakhch E, Bernard C, Hatem SN, Isnard R, Cluzel P, Le Feuvre C, Leprince P, Hammoudi N, Lemoine FM, Klatzmann D, Vicaut E, Komajda M, Montalescot G, Lompré AM, Hajjar RJ, AGENT-HF Investigators.
Effect of Intracoronary Administration of AAV1/SERCA2a on Ventricular Remodelling in Patients with Advanced Systolic Heart Failure: Results from the AGENT-HF Randomized Phase 2 Trial.
Eur J Heart Fail. 2017 Nov; 19 (11):1534-1541.

De Jong A, Carreira S, Na N, Carillion A, Jiang C, Beuvin M, Lacorte JM, Bonnefont-Rousselot D, Riou B, Coirault C.
Diaphragmatic function is enhanced in fatty and diabetic fatty rats.
PLoS One. 2017 Mar 22; 12(3).

Yaniz-Galende E, Roux M, Nadaud S, Mougenot N, Bouvet M, Claude O, Lebreton G, Blanc C, Pinet F, Atassi F, Perret C, Dierick F, Dussaud S, Leprince P, Trégouët DA, Marazzi G, Sassoon D, Hulot JS.
Fibrogenic Potential of *PW1/Peg3 expressing Cardiac Stem Cells.*
J Am Coll Cardiol. 2017 Aug 8; 70:728-41.

Launay T, Momken I, Carreira S, Mougenot N, Zhou XL, De Koning L, Niel R, Riou B, Billat V, Besse S.
Acceleration-based training: A new mode of training in senescent rats improving performance and left ventricular and muscle functions.
Exp Gerontol. 2017 Sep; 95:71-76.

Billat V, Dhonneur G, Mille-Hamard L, Le Moyec L, Momken I, Launay T, Koralsztein JP, Besse S.
Case Studies in Physiology: Maximal oxygen consumption and performance in a centenarian cyclist.
J Appl Physiol (1985). 2017 Mar 1; 122(3):430-434.

Niel R, Ayachi M, Mille-Hamard L, Le Moyec L, Savarin P, Clement MJ, Besse S, Launay T, Billat VL, Momken I
A new model of short acceleration-based training improves exercise performance in old mice.
Scand J Med Sci Sports. 2017 Dec;27(12):1576-1587.

Carillion A, Feldman S, Na N, Biais M, Carpentier W, Birenbaum A, Cagnard N, Loyer X, Bonnefont-Rousselot D, Hatem S, Riou B, Amour J.
Atorvastatin reduces β-Adrenergic dysfunction in rats with diabetic cardiomyopathy.
PLoS One. 2017 Jul 20; 12(7).

Eichel CA, Beuriot A, Chevalier MY, Rougier JS, Louault F, Dilanian G, Amour J, Coulombe A, Abriel H, Hatem SN, Balse E.
Lateral Membrane-Specific MAGUK CASK Down-Regulates NaV1.5 Channel in Cardiac Myocytes.
Circ Res. 2016 Aug 5; 119(4):544-56.

Jumeau C, Rupin A, Chieng-Yane P, Mougenot N, Zahr N, David-Dufilho M, Hatem SN.
Direct Thrombin Inhibitors Prevent Left Atrial Remodeling Associated With Heart Failure in Rats.
JACC Basic Transl Sci. 2016 1(5): 328-339.

Evin M, Redheuil A, Soulat G, Perdrix L, Ashrafpoor G, Giron A, Lamy J, Defrance C, Roux C, Hatem SN, Diebold B, Mousseaux E, Kachenoura N.
Left atrial aging: a cardiac magnetic resonance feature-tracking study.
Am J Physiol Heart Circ Physiol. 2016 Mar 1; 310(5):H542-9.

Lau DH, Schotten U, Mahajan R, Antic NA, Hatem SN, Pathak RK, Hendriks JM, Kalman JM, Sanders P.
Novel mechanisms in the pathogenesis of atrial fibrillation: practical applications.
Eur Heart J. 2016 May 21; 37(20): 1573-81.
Ghigna MR, Guignabert C, Montani D, Girerd B, Jaïs X, Savale L, Hervé P, Thomas de Montpréville V, Mercier O, Sitbon O, Soubrier F, Fadel E, Simonneau G, Humbert M, Dorfmüller P.
BMPR2 mutation status influences bronchial vascular changes in pulmonary arterial hypertension.
Eur Respir J. 2016 Dec; 48(6):1668-1681.

Bénard L, Oh JG, Cacheux M, Lee A, Nonnenmacher M, Matasic DS, Kohlbrenner E, Kho C, Pavoine C, Hajjar RJ, Hulot JS.
Cardiac Stim1 Silencing Impairs Adaptive Hypertrophy and Promotes Heart Failure Through Inactivation of mTORC2/Akt Signaling.
Circulation. 2016 Apr 12; 133(15):1458-71.

Levy M, Eyries M, Szezepanski I, Ladouceur M, Nadaud S, Bonnet D, Soubrier F.
Genetic analyses in a cohort of children with pulmonary hypertension.
Eur Respir J. 2016 Oct;48(4):1118-1126.

Dierick F, Héry T, Hoareau-Coudert B, Mougenot N, Monceau V, Claude C, Crisan M, Besson V, Dorfmüller P, Marodon G, Fadel E, Humbert M, Yaniz-Galende E, Hulot JS, Marazzi G, Sassoon D, Soubrier F, Nadaud S.
Resident PW1+ Progenitor Cells Participate in Vascular Remodeling During Pulmonary Arterial Hypertension.
Circ Res. 2016 Mar 4;118(5):822-33.

Venteclef N*, Guglielmi V*, Balse E, Gaborit B, Cotillard A, Atassi F, Amour J, Leprince P, Dutour A, Clément K, Hatem SN.
Human Epicardial Adipose Tissue Induces Fibrosis of the Atrial Myocardium through the Secretion of Adipo-fibrokines.
Eur Heart J. 2015 Apr 1; 36(13):795-805a.
*Equally contributors.

Gillet L, Rougier JS, Shy D, Sonntag S, Mougenot N, Essers M, Shmerling D, Balse E, Hatem SN, Abriel H.
Cardiac-specific ablation of synapse-associated protein SAP97 in mice decreases potassium currents but not sodium current.
Heart Rhythm. 2015 Jan;12(1):181-92.

Algalarrondo V, Wahbi K, Sebag F, Gourdon G, Bedlord C, Azibi K, Balse E, Coulombe A, Fischmeister R, Eymard B, Duboc D, Hatem SN.
Abnormal sodium current properties contribute to cardiac electrical and contractile dysfunction in a mouse model of myotonic dystrophy type 1.
Neuromuscul Disord. 2015 Apr;25(4):308-20.

Gaborit B, Venteclef N, Ancel P, Pelloux V, Gariboldi V, Leprince P, Amour J, Hatem SN, Jouve E, Dutour A, Clément K.
Human epicardial adipose tissue has a specific transcriptomic signature depending on its anatomical peri-atrial, peri-ventricular, or peri-coronary location.
Cardiovasc Res. 2015 Oct 1; 108 (1):62-73.

Jiang C, Carillion A, Na N, De Jong A, Feldman S, Lacorte J-M, Bonnefont-Rousselot D, Riou B, Amour J.
Modification of the β-Adrenoceptor Stimulation Pathway in Zucker Obese and Obese Diabetic Rat Myocardium.
Crit Care Med. 2015 Jul; 43 (7).

Michelet P, Carreira S, Demoule A, Amour J, Langeron O, Riou B, Coirault C. 2015.
Effects of Acute Respiratory and Metabolic Acidosis on Diaphragm Muscle Obtained from Rats.
Anesthesiology 2015 Apr; 122 (4): 876–83.

Carillion A, Feldman S, Jiang C, Atassi F, Na N, Mougenot N, Besse S, Hulot J-S, Riou B, Amour J.
Overexpression of Cyclic Adenosine Monophosphate Effluent Protein MRP4 Induces an Altered Response to β-Adrenergic Stimulation in the Senescent Rat Heart.
Anesthesiology 2015 Feb; 122 (2): 334–42.

Saliba Y, Keck M, Marchand A, Atassi F, Ouillé A, Cazorla O, Trebak M, Pavoine C, Lacampagne A, Hulot JS, Farès N, Fauconnier J, Lompré AM.
Emergence of Orai3 activity during cardiac hypertrophy.
Cardiovasc Res. 2015 Mar 1;105(3):248-59.

Huertas A, Tu L, Le Hiress M, Ricard N, Thuillet R, Phan C, Nadaud S, Fadel E, Humbert M, Guignabert C.
Leptin signalling system as a target for pulmonary alterial hypertension therapy.
Eur Resp J. 2015 Apr; 45(4):1066-80.

Huet E, Gabison E, Vallee B, Mougenot N, Linguet G, Riou B, Jarosz C, Menashi S, Besse S.
Deletion of extracellular matrix metalloproteinase inducer/CD147 induces altered cardiac extracellular matrix remodeling in aging mice.
J Physiol Pharmacol. 2015 Jun; 66(3):355-66.

Eyries M, Montani D, Girerd B, Perret C, Leroy A, Lonjou C, Chelghoum N, Coulet F, Bonnet D, Dorfmüller P, Fadel E, Sitbon O, Simonneau G, Tregouët DA, Humbert M, Soubrier F.
EIF2AK4 mutations cause pulmonary veno-occlusive disease, a recessive form of pulmonary hypertension.
Nat Genet. 2014 Jan;46(1):65-9.

Wan J, Benkdane M, Alons E, Lotersztajn S, Pavoine C.
M2 kupffer cells promote hepatocyte senescence: an IL-6-dependent protective mechanism against alcoholic liver disease.
Am J Pathol. 2014 Jun;184(6):1763-72.

Wan J, Benkdane M, Teixeira-Clerc F, Bonnafous S, Louvet A, Lafdil F, Pecker F, Tran A, Gual P, Mallat A, Lotersztajn S, Pavoine C.
M2 Kupffer cells promote M1 Kupffer cell apoptosis: a protective mechanism against alcoholic and nonalcoholic fatty liver disease.
Hepatology. 2014 Jan;59(1):130-42.

Hidalgo M, Marchant D, Quidu P, Youcef-Ali K, Richalet JP, Beaudry M, Besse S, Launay T.
Oxygen modulates the glutathione peroxidase activity during the L6 myoblast early differentiation process.
Cell Physiol Biochem. 2014 ; 33(1):67-77.

Boycott H, Barbier C, Eichel C, Costa K, Martins R, Louault F, Dilanian G, Coulombe A, Hatem SN, Balse E.
Shear stress triggers insertion of voltage-gated potassium channels from intracellular compartments in atrial myocytes.
Proc Natl Acad Sci USA, 2013 Oct 8; 110(41).

Merlet E, Lipskaia L., Marchand A., Hadri L., Mougenot N., Atassi F., Liang L., Hatem S.N., Hajjar R.J, Lompré A.-M. 2013.
A Calcium-Sensitive Promoter Construct for Gene Therapy.
Gene Therapy 2013 Mar; 20 (3): 248–54.

Ciumas M, Eyries M, Poirier O, Maugenre S, Dierick F, Gambaryan N, Montagne K, Nadaud S, Soubrier F.
Bone morphogenetic proteins protect pulmonary microvascular endothelial cells from apoptosis by upregulating α-B-crystallin.
Arterioscler Thromb Vasc Biol. 2013 Nov;33(11):2577-84.

Germain M, Eyries M, Montani D, Poirier O, Girerd B, Dorfmüller P, Coulet F, Nadaud S, Maugenre S, Guignabert C, Carpentier W, Vonk-Noordegraaf A, Lévy M, Chaouat A, Lambert JC, Bertrand M, Dupuy AM, Letenneur L, Lathrop M, Amouyel P, de Ravel TJ, Delcroix M, Austin ED, Robbins IM, Hemnes AR, Loyd JE, Berman-Rosenzweig E, Barst RJ, Chung WK, Simonneau G, Trégouët DA, Humbert M, Soubrier F.
Genome-wide association analysis identifies a susceptibility locus for pulmonary arterial hypertension.
Nat Genet. 2013 May;45(5):518-21.

Nadaud S, Poirier O, Girerd B, Blanc C, Montani D, Eyries M, Imbert-Bismut F, Pacheco A, Vigne J, Tregouet DA, Humbert M, Soubrier F.
Small platelet microparticle levels are increased in pulmonary arterial hypertension.
Eur J Clin Invest. 2013 Jan;43(1):64-71.

Merlet E, Atassi F, Motiani RK, Mougenot N, Jacquet A, Nadaud S, Capiod T, Trebak M, Lompré AM, Marchand A.
miR-424/322 regulates vascular smooth muscle cell phenotype and neointimal formation in the rat.
Cardiovasc Res. 2013 Jun 1; 98(3):458-68.

Besse S, Comte R, Fréchault S, Courty J, Joël de L, Delbé J.
Pleiotrophin promotes capillary-like sprouting from senescent aortic rings.
Cytokine. 2013 Apr; 62(1):44-7.

>

AWARDS

Stéphane Hatem
- Alain Castaigne award (2018)

Florent Soubrier
- Jean Valade award (2014)
- Lamonica Cardiology award - Académie des Sciences (2018)

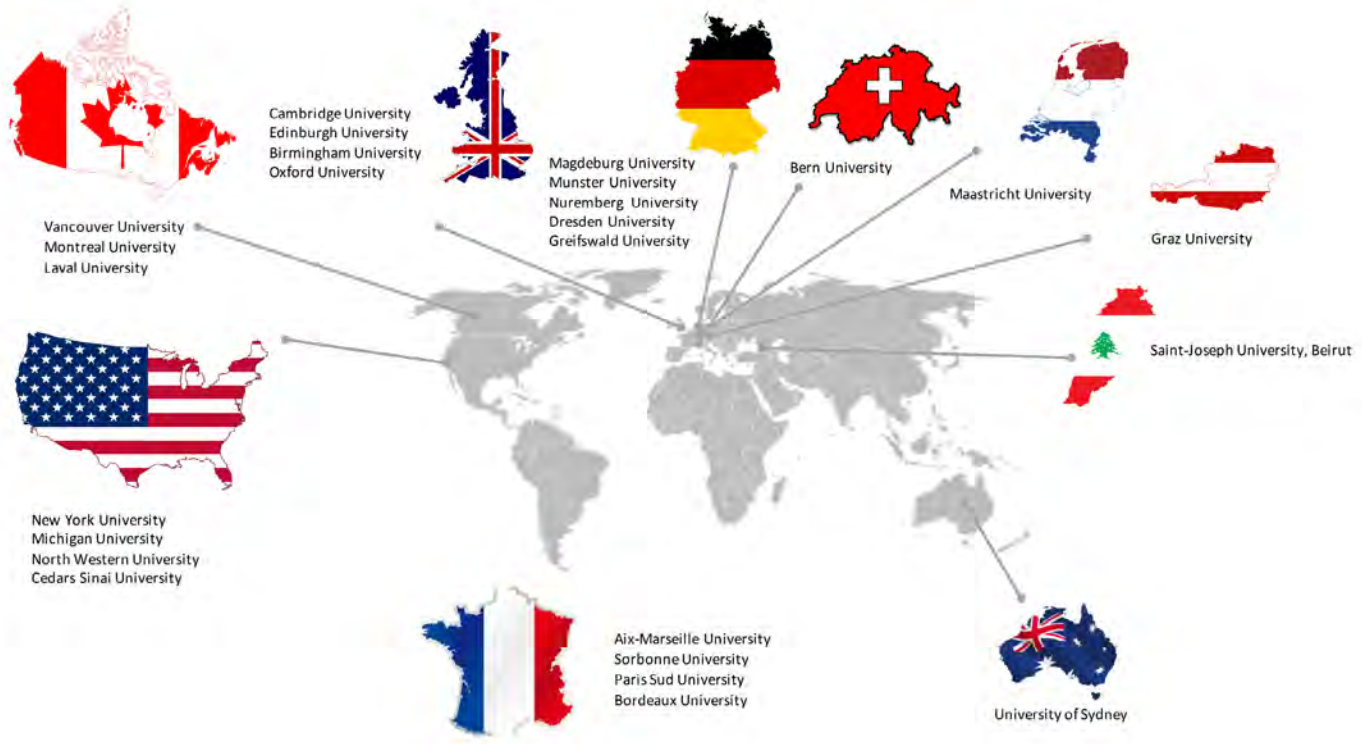
France Diérick
- Marion Elizabeth Brancher award (2017)

FUNDS

KEYWORDS

Cardiomyocyte, Vascular progenitor,, Epicardial progenitor cell,Macrophage,Endothelial cell, Smooth muscle cell, Fibroblast, Adipocyte, Atrial fibrillation, Heart failure, Cardiac hypertrophy, Pulmonary arterial hypertension, Pulmonary vascular occlusive disease, Fibrosis, Adipogenesis, Inflammation, Remodeling, Lineage tracing, Ion channels, GCN2, PW1, PDGFRalpha, TNFalpha, Fractalkine.

COLLABORATIONS



>

Team 4

CELLULAR AND SYSTEMIC LIPID METABOLISM IN CARDIOMETABOLIC DISEASES

THE TEAM

TEAM LEADER

Wilfried LE GOFF, *PhD, CR, Inserm*

INVESTIGATORS

Randa BITTAR, *PharmD, PH, AP-HP*
Olivier BLUTEAU, *PhD, AP-HP*
Eric BRUCKERT, *MD, PhD, PU-PH, AP-HP*
Alain CARRIE, MD, *PhD, PU-PH, AP-HP*
Martine GLORIAN, *MCU, SU*
Maryse GUERIN, *PhD, DR, Inserm*
Isabelle GUILLAS, *PhD, MCU, SU*
Anatol KONTUSH, *PhD, DR, Inserm*
Jean-Marc LACORTE, *MD, PhD, PU-PH, AP-HP*

TECHNICAL STAFF

Hervé DURAND, *IE, Inserm*
Eric FRISDAL, *PhD, IR, Inserm*
Sophie GALIER, *T, Inserm*

PHD STUDENTS

Véronica DAHIK RODAS
Alexandre MOTTE
Malik TARADEH
Clément MATERNE
Canelle REYDELLET

>

OBJECTIVES

Cardiovascular diseases (CVD) still remain the major cause of morbidity and mortality worldwide due to the growing prevalence of obesity and associated metabolic disorders, including insulin resistance and Type 2 diabetes. Dyslipidemia, characterized by altered circulating concentrations of lipoproteins and lipids is a major component in the development of cardiometabolic diseases (CMD). As a consequence, lipid-lowering therapies are the privileged therapeutic strategy in CMD. Mechanisms through which lipids contribute to the development of metabolic disorders are multiple and involve complex signaling and regulation pathways at the both cellular and systemic levels. Importantly, it is now clear that a large spectrum of lipid species not only restricted to cholesterol and triglycerides participates actively in alterations of lipid and lipoprotein metabolism in CMD. Then, deciphering of dysfunctional lipid metabolic pathways might help to propose new therapeutic targets to prevent or hamper the occurrence and development of CMD.

Our recent pioneering studies leading to the identification by omics approaches of lipid networks and metabolic pathways controlling biological activities of plasma lipoproteins and cell activation in CMD open up new insights in understanding how alterations in lipid metabolism contribute to CMD onset. In particular, our recent findings lead us to revisit the current understanding of atheroprotective high-density lipoprotein (HDL) and triglyceride-rich lipoprotein (TRL) metabolism and its role in CVD.

Building on tight interactions with clinical and valorization departments, our research program aims to propose new candidate pathways, genes and biomarkers in the context of CMD.

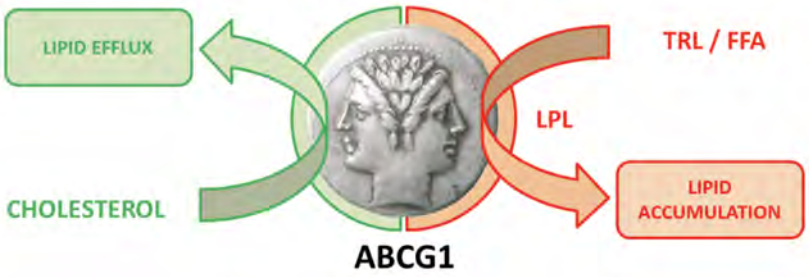
Wilfried Le Goff

RESEARCH PROJECTS

THEME 1 - DECIPHERING MOLECULAR MECHANISMS CONTROLLING CELL AND TISSUE LIPID HOMEOSTASIS IN CARDIOMETABOLIC DISEASES

W. LE GOFF

Maintenance of cellular lipid homeostasis is essential for preservation of tissue function especially in metabolic states characterized by a disturbance of lipid metabolism. Thus, alteration of lipid homeostasis in key metabolic tissues such as liver, adipose tissue and intestine, but also in vascular wall, is a frequent feature of cardiometabolic diseases (CMD). Macrophages are pivotal actors in the maintenance of tissue lipid homeostasis and activation of macrophages by bioactive lipids is a critical event in development and progression of these pathologies. Our previous works aiming the study of mechanisms governing macrophage lipid homeostasis uncovered a tight link between the membrane ATP-Binding Cassette G1 (ABCG1) lipid transporter and cellular triglyceride storage in CMD. Whereas we demonstrated that ABCG1 is not a significant actor in cholesterol efflux from human macrophages (Larrede S., 2009), this function being mostly carried by ABCA1 (Du XM, 2015), we identified a new role for ABCG1 in foam cell formation through the control of the bioavailability of lipoprotein lipase in macrophages (Olivier M., 2012). We extended our work in the context of obesity and revealed the contribution of adipose ABCG1 in triglyceride storage, fat mass growth and obesity in humans (Frisdal E., 2015). Importantly, the manipulation of ABCG1 brought to light the intimate link between sphingomyelin and triglycerides storage. We propose that ABCG1 could be a potential therapeutic target in obesity (PCT/EP2011/073140) and we are currently evaluating the impact of the ABCG1 targeting on diet-induced obesity and associated metabolic disorders.



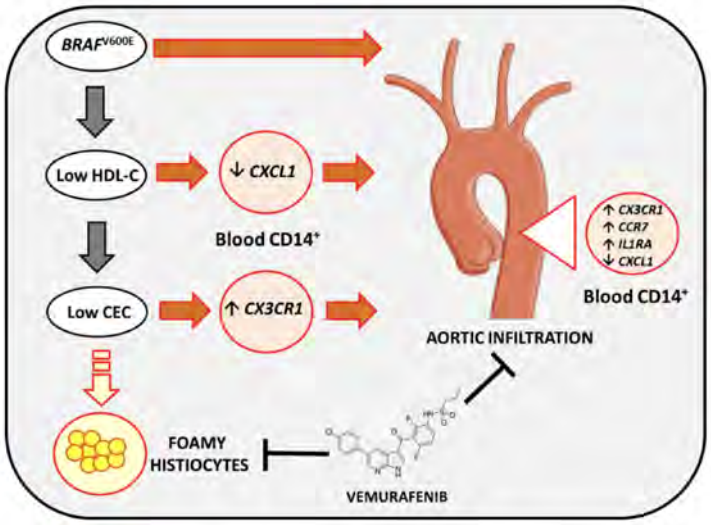
***ABCG1 is a Janus-faced metabolic switch**. In a cholesterol-rich metabolic context, ABCG1 protects from tissue lipid accumulation by promoting cellular free cholesterol efflux (left side of the Janus face). By contrast, ABCG1 promotes cellular lipid storage in a fat-rich environment by controlling lipoprotein lipase activity (right side of the Janus face). TRL: Triglyceride-rich lipoproteins, FFA: Free fatty acids, LPL: lipoprotein lipase. From Frisdal E. & Le Goff W. Adipocyte, 2015.*

Beyond sphingomyelin, sphingolipids and phospholipids have emerged as being intimately associated to the appearance of cardiometabolic disorders. However, the mechanisms through which those lipids exert their action in the context of CMD are complex and largely unknown. More specifically, sphingolipids and phospholipids are essential in the architecture of the membrane structure which is a critical pillar in macrophage functions. Dietary fatty acids can be metabolized into a range of sphingolipids and phospholipids species; however the impact as well as the precise mechanisms involved in such a rearrangement in macrophages are not yet elucidated. Building on the pioneering characterization of the lipidome and transcriptome of tissue macrophages in response to dietary lipids, our group aims to determine how the tissue and metabolic shaping of macrophages by sphingolipids and phospholipids contributes to the appearance of CMD disorders. This project will help to decipher the complex interactions between diet, lipid metabolism and metabolic diseases by delineating the cellular regulatory pathways by which sphingolipids and phospholipids exert their biological activities in the context of CMD. In addition, this project will allow the identification of potential new therapeutic targets as well as new circulating biomarkers in the treatment and the prevention of CMD.

THEME 2 - EXPLORATION OF THE CLOSE LINK BETWEEN HDL PHENOTYPE AND LIPID-LADEN MACROPHAGE / HISTIOCYTE FORMATION FOR THE IDENTIFICATION OF NEW PHYSIOPATHOLOGICAL PATHWAYS IN RARE HUMAN DISEASES

W. LE GOFF

Alteration of cellular lipid homeostasis is frequently observed in numerous pathologies although this latter does not result primarily from major defects of lipid metabolism but rather is a secondary clinical manifestation of the disease. Such a disturbance is associated with autoimmune or inflammatory diseases such as rheumatoid arthritis (RA), Systemic Lupus Erythematosus (SLE), Crohn's disease or sepsis which are characterized by a chronic inflammation and a high risk to develop atherosclerosis and cardiovascular diseases. One of the common features in those pathologies is the presence of low HDL levels which is associated in some cases with dysfunctional HDL, both could be markers of disease severity. Our studies on rare diseases exhibiting lipid depots in lipid-laden cells under the form of Touton cells or foamy histiocytes brought to light the major role of HDL in those pathologies in the absence of any hyperlipidemia. Indeed, we reported that the reduction of both levels and cholesterol efflux capacity of HDL particles in necrobiotic xanthogranuloma with monoclonal gammopathy (NXG) promotes macrophage lipid accumulation and could contribute to cholesterol depots into giant Touton cells observed in skin lesions characterizing NXG patients (Szalat R, 2014). Moreover, this low HDL phenotype was correlated to the unique inflammatory signature detected in NXG patients as well as to the proinflammatory phenotype of blood monocytes and to their potential ability to be recruited into skin lesions.



Proposed mechanisms for the lipid-laden histiocyte formation and the aortic infiltration in ECD. CEC: Cholesterol Efflux Capacity, From Aubart Cohen & al., 2018.

Our more recent works in Erdheim-Chester Disease (ECD), a rare form of non-Langerhans cell histiocytosis characterized by the infiltration of multiple tissues with foamy histiocytes, indicated that patients harboring the *BRAF*^{V600E} mutation exhibit a hypoalphalipoproteinemia and a reduced capacity to promote macrophage cholesterol efflux which could contribute to foamy histiocyte formation. More importantly, cardiovascular involvement is frequent in ECD and leads to a severe prognosis and our findings uncovered a major independent role of both *BRAF*^{V600E} and HDL in histiocyte infiltraton in aorta (Aubart-Cohen F, 2018).

THEME 3 - LIPID METABOLISM AND CARDIOVASCULAR RISK

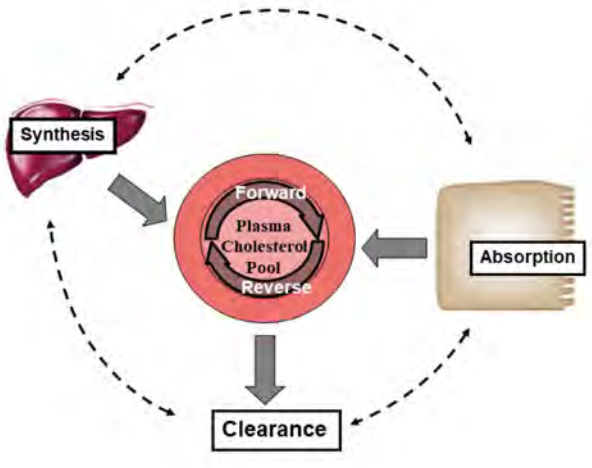
M. GUÉRIN

Despite aggressive low-density lipoprotein-cholesterol (LDL-C) reduction to therapeutic goals, a majority of patients remain at high cardiovascular risk, leaving CVD among the leading causes of death around the world. Thus inhibition of the endogenous synthesis of cholesterol should be combined with alternative therapeutic strategies targeting distinct metabolic pathways. The atheroprotective role of HDL particles is related to reverse cholesterol transport (RCT) pathway, which involves the centripetal movement of free cholesterol from peripheral tissues, to the liver. In man, we demonstrated the determinant role of Cholesterol Ester Transfer Protein (CETP) activity in the modulation of biological activities of HDL particles and in particular their capacity to mediate cholesterol efflux from human macrophages (Bellanger N. 2012; Villard E., 2013; El Khoury P., 2014). We defined an optimal range of CETP activity that may represent a future clinical therapeutic goal for endogenous CETP activity in patients with metabolic disorders at high CV risk (Villard E., 2012 and 2013). We demonstrated that the overall efficacy of the RCT pathway is altered in various metabolic disorders (El Khoury P., 2016) or inflammatory states (El Khoury P., 2015) and closely associated with clinical features of atherosclerosis (Gall J., 2016). More recently, we demonstrated that serum cholesterol efflux capacity, which reflects flow of cholesterol through multiple intravascular components of the reverse cholesterol transport process, is independently associated with long term survival in myocardial infarction patients (Guerin M., 2018). These findings identified serum cholesterol efflux capacity as a useful biomarker for identification of patients at higher risk of mortality after an acute coronary event. Improving/restoring serum cholesterol efflux capacity after an acute coronary event could potentially improve patient's prognosis. Such hypothesis is currently being tested in the large ongoing AEGIS-2 trial and supported by our findings.

Blood cholesterol is the result of input from gut absorption and endogenous synthesis, relative to clearance through hepatic and extrahepatic tissue pathways. The cholesterol metabolism is equally closely linked to bile acids metabolism as bile acids represent end-products of cholesterol that are excreted into feces which represent an additional pathway for the elimination of excess cholesterol. Physiological or pharmacological induced changes in one of these latter parameters directly impact the others suggesting that therapeutic strategies for reducing residual cardiovascular risk needs a multi-level approach.

We propose to focus on major metabolic pathways implicated in the determination of body cholesterol pool that include not only cholesterol synthesis and absorption but also its intravascular transport and fecal excretion.

Significance. Aggressive reduction of LDL-C has been the cornerstone of preventive CV care for hypercholesterolemic patients at high CV risk over recent decades. Improvement in the prevention and treatment of atherosclerosis over the past 25 years has made it possible to decrease the death rate from CVD approximately by half. However, in France, the number of deaths from CVD still amounts to almost 200,000 per year, thereby highlighting the need for identification of new and more personalized therapeutic strategies. The next decade will likely be oriented towards new approaches to reduce residual CV risk, based on the knowledge of cholesterol transport, metabolism and catabolism. A rational for combination therapies based on knowledge of the physiological pathways is necessary for a personalized medical care.



Major metabolic pathway determining the body cholesterol pool

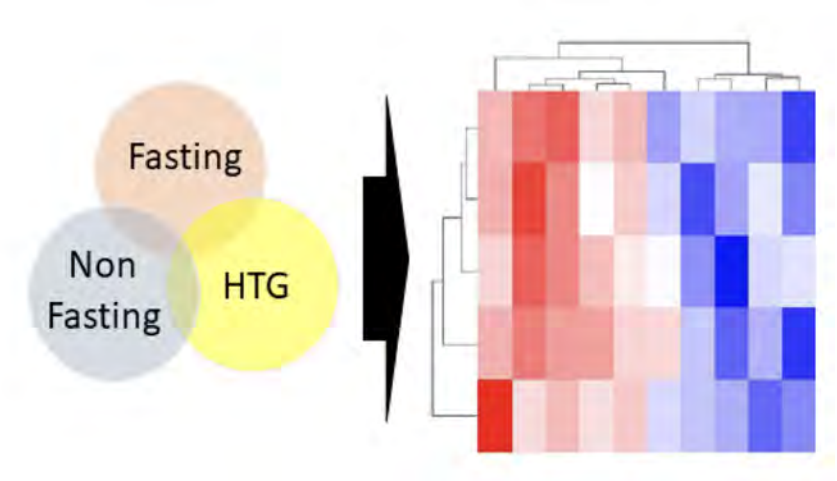
THEME 4 - POSTPRANDIAL STATE AND TRIGLYCERIDE RICH LIPOPROTEIN METABOLISM

J-M LACORTE, M. GUÉRIN

Postprandial lipid metabolism has received considerable attention since it was proposed that postprandial triglyceride-rich lipoproteins have been identified as a cardiovascular risk factor, however very few studies on postprandial lipid metabolism have been conducted. The intimate relationship between postprandial lipemia and atherosclerosis clearly suggests that the relationship between lipoprotein metabolism and atherosclerosis can no longer be considered exclusively on the basis of fasting lipid levels. An exaggerated postprandial lipemia represents a frequent metabolic abnormality of a number of lifestyle-related diseases associated with increased morbidity and mortality. Postprandial metabolism involves several organs and numerous hormones that some are dysregulated in obese or diabetic patients. In consequence identification of factors that interfere with postprandial lipoprotein metabolism is of major interest.

Transient elevation of triglyceridemia represents the first and main marker of postprandial metabolism reflecting occurrence and accumulation of triglyceride-rich lipoproteins. Thus, plasma triglyceride is the first marker used in postprandial studies. However, postprandial metabolism is equally associated with an intense intravascular remodeling of all classes of plasma lipoprotein particles. Our objective is to explore the impact of postprandial lipemia on quantitative and qualitative modification of intravascular lipoproteins of both intestinal and liver origin as well as on their anti- or pro-atherogenic properties. By high-throughput array analysis we recently identified several miRs that are differentially expressed during postprandial phase. These entirely original observations represent the first evidence that a variation of circulating miRNAs during postprandial phase is associated with a miRNAs signature that may differ according the metabolic context. We aim to determine whether postprandial miRs variations contribute into the development of CMD associated with premature atherosclerosis or might represent biomarkers of metabolic diseases.

Significance. The project will afford new insights in the comprehension of mechanisms underlying the relationship between postprandial hypertriglyceridemia and cardiovascular risk.



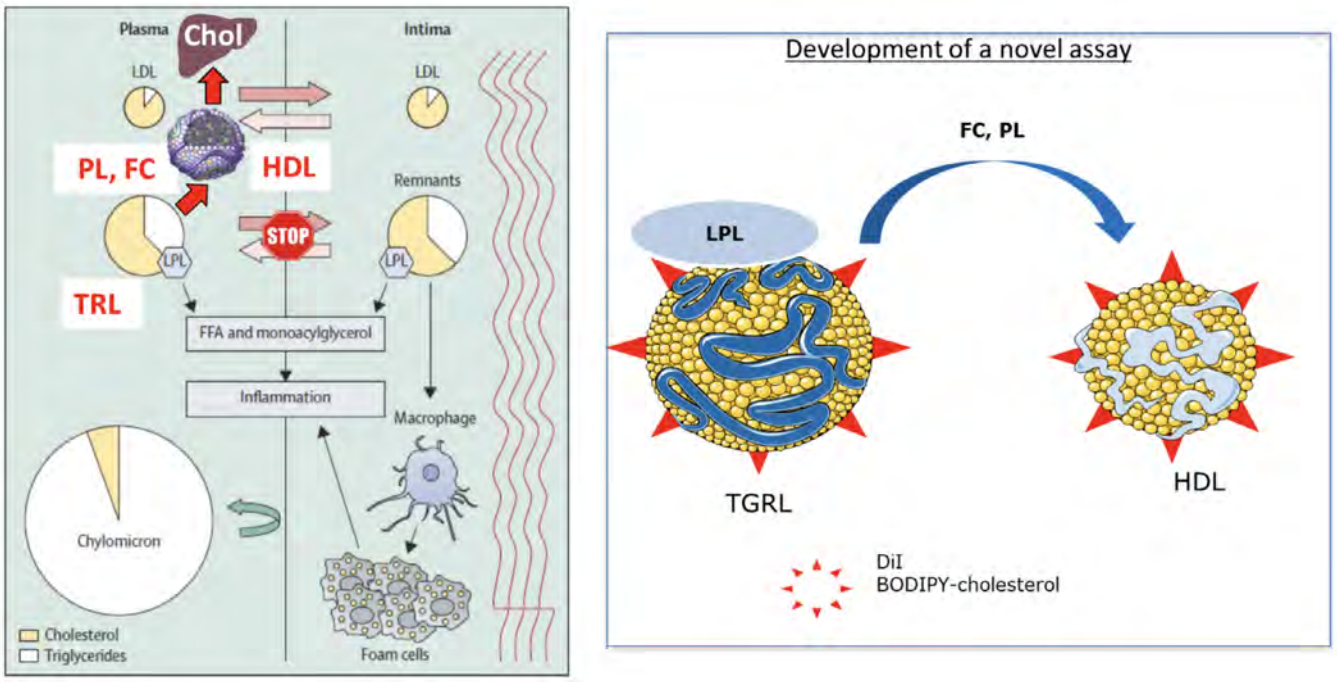
Differential postprandial miR expression according to the metabolic context (Guérin M & Lacorte J.-M, 2018, unpublished observations).

THEME 5 - REVISITING THE PRESENT CONCEPT OF HDL METABOLISM

A. KONTUSH

Decreased plasma levels of HDL-C are established as an independent CV risk factor. This association may reflect multiple atheroprotective properties of HDL particles, including cellular cholesterol efflux from macrophages together with numerous other activities. However, large-scale clinical studies aimed to reduce CV events by raising HDL-C concentrations have failed repeatedly. Indeed, although CETP inhibitors are highly effective for increasing HDL-C (up to +150%), clinical trials of these agents brought about predominantly negative results. Furthermore, data obtained using Mendelian randomisation do not support a causal relationship between HDL-C and CV risk. Such major controversy needs to be resolved in order to allow further development of cardiovascular therapies. It is important in this regard that our recent data show that increased HDL-C levels may be paradoxically associated with increased risk of CV disease. Indeed, we found, in collaboration with other international and national teams, that a mutation of SR-BI receptor that increases HDL-C levels also paradoxically increases coronary heart disease (Zanoni, 2016).

The sources of HDL-C in the circulation are of a key importance to clarify the relationship between HDL and CV disease. A large part of HDL-C is derived, in a form of free cholesterol, from triglyceride-rich lipoproteins (TGRL), including chylomicrons and very-low density lipoproteins (VLDL), upon their lipolysis by lipoprotein lipase (LPL). This process is greatly enhanced in the postprandial phase when circulating TG levels are elevated via secretion of chylomicrons but is also active in the interprandial state. Surface fragments (free cholesterol, phospholipids, apolipoproteins) of TGRL liberated during the lipolysis add to the circulating HDL pool; ensuing esterification of free cholesterol by LCAT expands HDL particles with a formation of lipophilic core. Importantly, cholesterol efflux from peripheral cells, including macrophages, which is presently considered to represent the major anti-atherogenic activity of HDL, provides only a minor contribution to HDL-C levels, which is greatly inferior to that of TGRL lipolysis.



HDL prevents surface TRL remnants from accumulation in the arterial wall via acquiring phospholipid (PL) and free cholesterol (FC) during TG lipolysis (left panel). An in vitro fluorescence-based assay to evaluate the capacity of HDL to acquire PL and FC from TRL upon LPL-mediated lipolysis (right panel).

Based on these data, we propose a working hypothesis that HDL plays a major role in the both post- and interprandial lipid metabolism, ensuring acquirement and transport of surface fragments generated during lipolysis of TGRL. Such lipid acceptor activity coupled to the transport of TGRL-derived surface lipids to the liver may represent a major function of HDL, which is presently overlooked by the mainstream research. As a corollary, HDL-C is an imperfect static measure of this dynamic pathway. In particular, low HDL-C levels associated with elevated CV risk may reflect insufficient cholesterol flux from TGRL to HDL upon lipolysis, resulting in the accumulation of cholesterol in pro-atherogenic TGRL remnants and in the development of CV disease. Lipid acceptor activity of HDL should therefore be diminished in low HDL-C subjects at elevated CV risk.

The major objective of this project is to evaluate the role of HDL in the post- and interprandial lipid metabolism as an acceptor of surface lipids liberated during lipolysis of TGRL. To achieve this goal, we primarily use a novel assay to measure lipid-accepting capacity of HDL under conditions of LPL-induced TGRL lipolysis in vitro, which was recently developed in our laboratory (European Patent EP17306042). We study mechanisms underlying the transfer of surface lipids from TGRL to HDL upon LPL-mediated lipolysis. The lipid-accepting capacity of HDL is investigated at the molecular level using modern proteomic, lipidomic and glycomic approaches to provide key information on structure-function relationships in HDL particles in both normal subjects and in patients with metabolic and CV diseases (acute MI, stable coronary disease, Type 2 diabetes, metabolic syndrome). This research is aimed at establishing clinical relevance of the assay to improve existing lipid-targeting therapies.

SELECTED PUBLICATIONS

Amarenco P, Kim JS, Labreuche J, Charles H, Abtan J, Béjot Y, Cabrejo L, Cha JK, Ducrocq G, Giroud M, Guidoux C, Hobeanu C, Kim YJ, Lapergue B, Lavallée PC, Lee BC, Lee KB, Leys D, Mahagne MH, Meseguer E, Nighoghossian N, Pico F, Samson Y, Sibon I, Steg PG, Sung SM, Touboul PJ, Touzé E, Varenne O, Vicaut É, Yelles N, Bruckert E; Treat Stroke to Target Investigators.
A Comparison of Two LDL Cholesterol Targets after Ischemic Stroke.
N Engl J Med. 2019.

Ma F., Darabi M., Tubeuf E., Canicio A., Lhomme M., Matheron L., Frisdal E., Lebreton S., Rached F., Ponnaiah M., Serrano C.V., Santos R.D., Brites F., Bolbach G., Gautier E., Huby T., Carrié A., Bruckert E., Guérin M., Couvert P., Giral P., Lesnik P., Le Goff W., Guillas I., Kontush A.
Free cholesterol transfer to high-density lipoprotein (HDL) upon triglyceride lipolysis underlies the U-shape relationship between HDL-cholesterol and cardiovascular disease.
European Journal of Preventive Cardiology. 2019.

Witztum JL, Gaudet D, Freedman SD, Alexander VJ, Digenio A, Williams KR, Yang Q, Hughes SG, Geary RS, Arca M, Stroes ESG, Bergeron J, Soran H, Civeira F, Hemphill L, Tsimikas S, Blom DJ, O'Dea L, Bruckert E.
Volanesorsen and Triglyceride Levels in Familial Chylomicronemia Syndrome.
N Engl J Med. 2019 Aug 8;381(6):531-542.

Guerin M, Silvain J, Gall J, Darabi M, Berthet M, Frisdal E, Hauguel-Moreau M, Zeitouni M, Kerneis M, Lattuca B, Brugier D, Collet JP, Lesnik P, Montalescot G.
Association of Serum Cholesterol Efflux Capacity With Mortality in Patients With ST-Segment Elevation Myocardial Infarction.
J Am Coll Cardiol. 2018 Dec 25;72(25):3259-3269.

Cohen-Aubart F., Guerin M., Poupel L., Cluzel P., Saint-Charles F., Charlotte F., Arsafi Y., Emile J-F., Frisdal E., Le Goff C., Donadieu J., Amoura Z., Lesnik P., Haroche J. & Le Goff W.
Hypoalphalipoproteinemia and BRAFV600E mutation are major predictors of aortic infiltration in the Erdheim-Chester Disease.
Arterioscler Thromb Vasc Biol. 2018; 38(8):1913-1925.

El Khoury P, Couvert P, Elbitar S, Ghaleb Y, Abou-Khalil Y, Azar Y, Ayoub C, Superville A, Guérin M, Rabès JP, Varret M, Boileau C, Jambart S, Giral P, Carrié A, Le Goff W*, Abifadel M*.
Identification of the first Tangier disease patient in Lebanon carrying a new pathogenic variant in ABCA1.
J. Clin. Lipidol. 2018;12(6):1374-1382.
*Equally contributors.

Rabès JP, Béliard S, Carrié A.
Familial hypercholesterolemia: experience from France.
Curr. Opin. Lipidol. 2018;29(2):65-71.

Perségol L, Darabi M, Dauteuille C, Lhomme M, Chantepie S, Rye KA, Therond P, Chapman MJ, Salvayre R, Nègre-Salvayre A, Lesnik P, Monier S, Kontush A.
Small dense HDLs display potent vasorelaxing activity, reflecting their elevated content of sphingosine-1-phosphate.
J. Lipid Res. 2018;59(1):25-34.

Sturm AC, Knowles JW, Gidding SS, Ahmad ZS, Ahmed CD, Ballantyne CM, Baum SJ, Bourbon M, Carrié A, Cuchel M, de Ferranti SD, Defesche JC, Freiberger T, Hershberger RE, Hovingh GK, Karayan L, Kastelein JJP, Kindt I, Lane SR, Leigh SE, Linton MF, Mata P, Neal WA, Nordestgaard BG, Santos RD, Harada-Shiba M, Sijbrands EJ, Stitziel NO, Yamashita S, Wilemon KA, Ledbetter DH, Rader DJ;
Convened by the Familial Hypercholesterolemia Foundation. Clinical Genetic Testing for Familial Hypercholesterolemia: JACC Scientific Expert Panel.
J. Am. Coll. Cardiol. 2018;72(6):662-680.

Gomez Rosso L, Lhomme M, Meroño T, Dellepiane A, Sorroche P, Hedjazi L, Zakiev E, Sukhorukov V, Orekhov A, Gasparri J, Chapman MJ, Brites F, Kontush A.
Poor glycemic control in type 2 diabetes enhances functional and compositional alterations of small, dense HDL3c. Biochim. Biophys.
Acta Mol. Cell. Biol. Lipids. 2017;1862(2):188-195.

Hussein H, Saheb S, Couturier M, Atassi M, Orsoni A, Carrié A, Therond P, Chantepie S, Robillard P, Bruckert E, Chapman MJ, Kontush A.
Small, dense high-density lipoprotein 3 particles exhibit defective antioxidative and anti-inflammatory function in familial hypercholesterolemia: Partial correction by low-density lipoprotein apheresis.
J. Clin. Lipidol. 2016;10(1):124-33.

Zanoni P, Khetarpal SA, Larach DB, Hancock-Cerutti WF, Millar JS, Cuchel M, DerOhannessian S, Kontush A, Surendran P, Saleheen D, Trompet S, Jukema JW, De Craen A, Deloukas P, Sattar N, Ford I, Packard C, Majumder Aa, Alam DS, Di Angelantonio E, Abecasis G, Chowdhury R, Erdmann J, Nordestgaard BG, Nielsen SF, Tybjærg-Hansen A, Schmidt RF, Kuulasmaa K, Liu DJ, Perola M, Blankenberg S, Salomaa V, Männistö S, Amouyel P, Arveiler D, Ferrieres J, Müller-Nurasyid M, Ferrario M, Kee F, Willer CJ, Samani N, Schunkert H, Butterworth AS, Howson JM, Peloso GM, Stitziel NO, Danesh J, Kathiresan S, Rader DJ;
CHD Exome+ Consortium; CARDIoGRAM Exome Consortium; *Global Lipids Genetics Consortium. Rare variant in scavenger receptor BI raises HDL cholesterol and increases risk of coronary heart disease.*
Science. 2016;351(6278):1166-71.

Didichenko SA, Navdaev AV, Cukier AM, Gille A, Schuetz P, Spycher MO, Thérond P, Chapman MJ, Kontush A, Wright SD.
Enhanced HDL Functionality in Small HDL Species Produced Upon Remodeling of HDL by Reconstituted HDL, CSL112: Effects on Cholesterol Efflux, Anti-Inflammatory and Antioxidative Activity.
Circ Res. 2016;119(6):751-63.

Rosenson RS, Brewer HB Jr, Ansell BJ, Barter P, Chapman MJ, Heinecke JW, Kontush A, Tall AR, Webb NR.
Dysfunctional HDL and atherosclerotic cardiovascular disease.
Nat. Rev. Cardiol. 2016;13(1):48-60.

Nissen SE, Stroes E, Dent-Acosta RE, Rosenson RS, Lehman SJ, Sattar N, Preiss D, Bruckert E, Ceska R, Lepor N, Ballantyne CM, Gouni-Berthold I, Elliott M, Brennan DM, Wasserman SM, Somaratne R, Scott R, Stein EA and Investigators G-.
Efficacy and Tolerability of Evolocumab vs Ezetimibe in Patients With Muscle-Related Statin Intolerance: The GAUSS-3 Randomized Clinical Trial.
JAMA. 2016;315:1580-90.

Gall J, Frisdal E, Bittar R, Le Goff W, Bruckert E, Lesnik P, Guerin M, Giral P.
Association of Cholesterol Efflux Capacity With Clinical Features of Metabolic Syndrome: Relevance to Atherosclerosis.
J. Am. Heart Assoc. 2016;5(12).

El Khoury P, Waldmann E, Huby T, Gall J, Couvert P, Lacorte JM, Chapman J, Frisdal E, Lesnik P, Parhofer KG, Le Goff W, Guerin M.
Extended-Release Niacin/Laropiprant Improves Overall Efficacy of Postprandial Reverse Cholesterol Transport.
Arterioscler Thromb Vasc Biol. 2016;36(2):285-94.

Valleix S, Verona G, Jourde-Chiche N, Nédelec B, Mangione PP, Bridoux F, Mangé A, Dogan A, Goujon JM, Lhomme M, Dauteuille C, Chabert M, Porcari R, Waudby CA, Relini A, Talmud PJ, Kovrov O, Olivecrona G, Stoppini M, Christodoulou J, Hawkins PN, Grateau G, Delpech M, Kontush A, Gillmore JD, Kalopissis AD, Bellotti V.
D25V apolipoprotein C-III variant causes dominant hereditary systemic amyloidosis and confers cardiovascular protective lipoprotein profile.
Nat. Commun. 2016;7:10353.

Le Goff C., Rogers C., Le Goff W., Pinto G., Bonnet D., Chrabieh M., Bole C., Nischke P., Picard C., Cormier-Daire V.
Heterozygous mutations in MAP3K7, encoding Transforming Growth Factor β Activated Kinase 1, cause CardioSpondyloCarpoFacial syndrome.
Am. J. Hum. Genet. 2016;99(2):407-13.

Darabi M, Guillas-Baudouin I, Le Goff W, Chapman MJ, Kontush A.
Therapeutic applications of reconstituted HDL: When structure meets function. Pharmacol.
Ther. 2016;157:28-42.

Du X., Kim M-J., Hou L., Le Goff W., Chapman M.J., van Eck M., Curtiss L.K., Burnett J., Cartland S.P., Quinn C.M., Kockx M., Kontush A.*, Rye K.A.*, Kritharides L*., Jessup W.*
HDL Particle Size is a Critical Determinant of ABCA1-Mediated Macrophage Cellular Cholesterol Export.
Circ. Res. 2015;116(7):1133-1142.
*Equally contributors.

Frisdal E., Le Lay S., Hooton H., Poupel L., Olivier M., Alili R., Plengpanich W., Villard E., Gilibert S., Lhomme M., Superville A., Miftah-Alkhair L., Chapman M.J., Dallinga-Thie G., Venteclef N., Poitou C., Tordjman J., Lesnik P., Kontush A., Huby T., Dugail I., Clement K., Guerin M., Le Goff W.
Adipocyte ATP-Binding Cassette G1 promotes triglyceride storage, fat mass growth and human obesity.
Diabetes. 2015;64(3):840-855.

Anjani K, Lhomme M, Sokolovska N, Poitou C, Aron-Wisnewsky J, Bouillot JL, Lesnik P, Bedossa P, Kontush A, Clement K, Dugail I, Tordjman J.
Circulating phospholipid profiling identifies portal contribution to NASH signature in obesity.
J. Hepatol. 2015;62(4):905-12.

Wiegman A, Gidding SS, Watts GF, Chapman MJ, Ginsberg HN, Cuchel M, Ose L, Averna M, Boileau C, Boren J, Bruckert E, Catapano AL, Defesche JC, Descamps OS, Hegele RA, Hovingh GK, Humphries SE, Kovanen PT, Kuivenhoven JA, Masana L, Nordestgaard BG, Pajukanta P, Parhofer KG, Raal FJ, Ray KK, Santos RD, Stalenhoef AF, Steinhagen-Thiessen E, Stroes ES, Taskinen MR, Tybjaerg-Hansen A, Wiklund O and European Atherosclerosis Society Consensus P. *Familial hypercholesterolaemia in children and adolescents: gaining decades of life by optimizing detection and treatment.*
Eur. Heart J. 2015;36:2425-37.

Rached F, Lhomme M, Camont L, Gomes F, Dauteuille C, Robillard P, Santos RD, Lesnik P, Serrano CV Jr, Chapman MJ, Kontush A.
Defective functionality of small, dense HDL3 subpopulations in ST segment elevation myocardial infarction: Relevance of enrichment in lysophosphatidylcholine, phosphatidic acid and serum amyloid A.
Biochim. Biophys. Acta. 2015;1851(9):1254-61.

Szalat R., Pirault J., Fermand J-P., Carrié A., Saint-Charles F., Olivier M., Robillard P., Cathébras P., Frisdal E., Villard E.F., Bruckert E., Chapman M.J., Giral P., Guerin M., Lesnik P., Le Goff W.
Physiopathology of Necrobiotic Xanthogranuloma with Monoclonal Gammopathy.
J. Intern. Med. 2014; 276(3): 269-284.

Rached F, Santos RD, Camont L, Miname MH, Lhomme M, Dauteuille C, Lecocq S, Serrano CV Jr, Chapman MJ, Kontush A.
Defective functionality of HDL particles in familial apoA-I deficiency: relevance of alterations in HDL lipidome and proteome.
J. Lipid Res. 2014;55(12):2509-20.

Hegele RA, Ginsberg HN, Chapman MJ, Nordestgaard BG, Kuivenhoven JA, Averna M, Boren J, Bruckert E, Catapano AL, Descamps OS, Hovingh GK, Humphries SE, Kovanen PT, Masana L, Pajukanta P, Parhofer KG, Raal FJ, Ray KK, Santos RD, Stalenhoef AF, Stroes E, Taskinen MR, Tybjaerg-Hansen A, Watts GF, Wiklund O and European Atherosclerosis Society Consensus P.
The polygenic nature of hypertriglyceridaemia: implications for definition, diagnosis, and management.
Lancet Diabetes Endocrinol. 2014;2:655-66.

Kingwell BA, Chapman MJ, Kontush A, Miller NE.
HDL-targeted therapies: progress, failures and future.
Nat. Rev. Drug Discov. 2014 Jun;13(6):445-64.

Cuchel M, Bruckert E, Ginsberg HN, Raal FJ, Santos RD, Hegele RA, Kuivenhoven JA, Nordestgaard BG, Descamps OS, Steinhagen-Thiessen E, Tybjaerg-Hansen A, Watts GF, Averna M, Boileau C, Boren J, Catapano AL, Defesche JC, Hovingh GK, Humphries SE, Kovanen PT, Masana L, Pajukanta P, Parhofer KG, Ray KK, Stalenhoef AF, Stroes E, Taskinen MR, Wiegman A, Wiklund O, Chapman MJ and European Atherosclerosis Society Consensus Panel on Familial H.
Homozygous familial hypercholesterolaemia: new insights and guidance for clinicians to improve detection and clinical management. A position paper from the Consensus Panel on Familial Hypercholesterolaemia of the European Atherosclerosis Society.
Eur. Heart J. 2014;35:2146-57.

Stroes E, Colquhoun D, Sullivan D, Civeira F, Rosenson RS, Watts GF, Bruckert E, Cho L, Dent R, Knusel B, Xue A, Scott R, Wasserman SM, Rocco M and Investigators G-.
Anti-PCSK9 antibody effectively lowers cholesterol in patients with statin intolerance: the GAUSS-2 randomized, placebo-controlled phase 3 clinical trial of evolocumab.
J. Am. Coll. Cardiol. 2014;63:2541-8.

Villard EF, El Khoury P, Frisdal E, Bruckert E, Clement K, Bonnefont-Rousselot D, Bittar R, Le Goff W, Guerin M.
Genetic determination of plasma cholesterol efflux capacity is gender-specific and independent of HDL-cholesterol levels.
Arterioscler. Thromb. Vasc. Biol. 2013;33(4):822-8.

Camont L, Lhomme M, Rached F, Le Goff W, Nègre-Salvayre A, Salvayre R, Calzada C, Lagarde M, Chapman MJ, Kontush A.
Small, dense high-density lipoprotein-3 particles are enriched in negatively charged phospholipids: relevance to cellular cholesterol efflux, antioxidative, antithrombotic, anti-inflammatory, and antiapoptotic functionalities.
Arterioscler. Thromb. Vasc. Biol. 2013;33(12):2715-23.

Rosenson RS, Brewer HB Jr, Ansell B, Barter P, Chapman MJ, Heinecke JW, Kontush A, Tall AR, Webb NR.
Translation of high-density lipoprotein function into clinical practice: current prospects and future challenges.
Circulation. 2013;128(11):1256-67.

Silbernagel G, Chapman MJ, Genser B, Kleber ME, Fauler G, Scharnagl H, Grammer TB, Boehm BO, Makela KM, Kahonen M, Carmena R, Rietzschel ER, Bruckert E, Deanfield JE, Miettinen TA, Raitakari OT, Lehtimaki T and Marz W.
High intestinal cholesterol absorption is associated with cardiovascular disease and risk alleles in ABCG8 and ABO: evidence from the LURIC and YFS cohorts and from a meta-analysis.
J. Am. Coll. Cardiol. 2013;62:291-9.

Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, Wiklund O, Hegele RA, Raal FJ, Defesche JC, Wiegman A, Santos RD, Watts GF, Parhofer KG, Hovingh GK, Kovanen PT, Boileau C, Averna M, Boren J, Bruckert E, Catapano AL, Kuivenhoven JA, Pajukanta P, Ray K, Stalenhoef AF, Stroes E, Taskinen MR, Tybjaerg-Hansen A and European Atherosclerosis Society Consensus P.
Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society.
Eur. Heart J. 2013;34:3478-90.

Olivier M., Tanck M.W., Out R., Villard E.F., Lammers B., Bouchareychas L., Frisdal E., Superville A., Van Berkel T., Kastelein J.J., Van Eck M., Jukema J.W., Chapman M.J., Dallinga-Thie G.M., Guerin M., Le Goff W.
Human ABCG1 controls macrophage LPL bioavailability and promotes foam cell formation.
Arterioscler. Thromb. Vasc. Biol. 2012;32:2223-2231.

Villard EF, El Khoury P, Duchene E, Bonnefont-Rousselot D, Clement K, Bruckert E, Bittar R, Le Goff W, Guerin M.
Elevated CETP activity improves plasma cholesterol efflux capacity from human macrophages in women.
Arterioscler. Thromb. Vasc. Biol.2012;32(10):2341-9.

Le Goff C., Mahaut C., Abhyankar A., Le Goff W., Serre V., Afenjar A., Destrée A., Di Rocco M., Héron D., Jacquemont S., Marlin S., Simon M., Tolmie J., Verloes A., Casanova J-L., Munnich A., Cormier-Daire V.
Mutations at a single codon in Mad Homology 2 domain of SMAD4 cause Myhre syndrome.
Nat. Genet., 2012; 44(1):85-88.

Guerin M.
Reverse cholesterol transport in familial hypercholesterolemia.
Curr. Opin. Lipidol. 2012;23(4):377-85.

Bourron O, Chebbi F, Halbron M, Saint-Martin C, Bellanne-Chantelot C, Abed A, Charbit B, Magnan C, Lacorte JM and Hartemann A.
Incretin effect of glucagon-like peptide 1 receptor agonist is preserved in presence of ABCC8/SUR1 mutation in beta-cell.
Diabetes Care. 2012;35.

Genser B, Silbernagel G, De Backer G, Bruckert E, Carmena R, Chapman MJ, Deanfield J, Descamps OS, Rietzschel ER, Dias KC and Marz W. Plant sterols and cardiovascular disease: a systematic review and meta-analysis. Eur. Heart J. 2012;33:444-51

Bellanger N, Orsoni A, Julia Z, Fournier N, Frisdal E, Duchene E, Bruckert E, Carrie A, Bonnefont-Rousselot D, Pirault J, Saint-Charles F, Chapman MJ, Lesnik P, Le Goff W*, Guerin M.*
Atheroprotective reverse cholesterol transport pathway is defective in familial hypercholesterolemia.
Arterioscler. Thromb. Vasc. Biol. 2011;31(7):1675-81.
*Equally contributors.

Camont L, Chapman MJ, Kontush A.
Biological activities of HDL subpopulations and their relevance to cardiovascular disease.
Trends Mol. Med. 2011;17(10):594-603.

Frisdal E., Lesnik P., Olivier M., Robillard P., Chapman M.J., Guérin M, Le Goff W.
Interleukin-6 protects human macrophages from cellular cholesterol accumulation and attenuates the pro-inflammatory response.
J. Biol. Chem. 2011;286(35): 30926-30936.

Huang R, Silva RA, Jerome WG, Kontush A, Chapman MJ, Curtiss LK, Hodges TJ, Davidson WS.
Apolipoprotein A-I structural organization in high-density lipoproteins isolated from human plasma.
Nat. Struct. Mol. Biol. 2011;18(4):416-22.

Aron-Wisnewsky J, Julia Z, Poitou C, Bouillot JL, Basdevant A, Chapman MJ, Clement K, Guerin M.
Effect of bariatric surgery-induced weight loss on SR-BI-, ABCG1-, and ABCA1-mediated cellular cholesterol efflux in obese women.
J. Clin. Endocrinol. Metab. 2011;96(4):1151-9.

Baldassarre D, Nyyssönen K, Rauramaa R, de Faire U, Hamsten A, Smit AJ, Mannarino E, Humphries SE, Giral P, Grossi E, Veglia F, Paoletti R, Tremoli E;IMPROVE study group.
Cross-sectional analysis of baseline data to identify the major determinants of carotid intima-media thickness in a European population:the IMPROVE study.
Eur. Heart J. 2010;31(5):614-22.

Chapman MJ, Le Goff W, Guerin M, Kontush A.
Cholesteryl ester transfer protein: at the heart of the action of lipid-modulating therapy with statins, fibrates, niacin, and cholesteryl ester transfer protein inhibitors.
Eur. Heart J. 2010;31(2):149-64.

Davidson WS, Silva RA, Chantepie S, Lagor WR, Chapman MJ, Kontush A.
Proteomic analysis of defined HDL subpopulations reveals particle-specific protein clusters: relevance to antioxidative function.
Arterioscler. Thromb. Vasc. Biol. 2009;29(6):870-6.

Larrède S., Quinn C.M., Jessup W., Frisdal E., Olivier M., Hsieh V., Kim M., Van Eck M., Couvert P., Carrié A., Giral P., Chapman M.J., Guérin M, Le Goff W.
Stimulation of cholesterol efflux by LXR agonists in cholesterol-loaded human macrophages is ABCA1-dependent but ABCG1-independent.
Arterioscler. Thromb. Vasc. Biol. 2009;29:1930-1936.

Catalano G, Julia Z, Frisdal E, Vedie B, Fournier N, Le Goff W, Chapman MJ, Guerin M.
Torcetrapib differentially modulates the biological activities of HDL2 and HDL3 particles in the reverse cholesterol transport pathway.
Arterioscler Thromb Vasc Biol. 2009;29(2):268-75.
Guerin M, Le Goff W, Duchene E, Julia Z, Nguyen T, Thuren T, Shear CL, Chapman MJ.
Inhibition of CETP by torcetrapib attenuates the atherogenicity of postprandial TG-rich lipoproteins in type IIB hyperlipidemia.
Arterioscler. Thromb. Vasc. Biol. 2008;28(1):148-54.

Out R.*, Jessup W.*, Le Goff W.*, Hoekstra M., Gelissen I.C., Zhao Y., Kritharides L., Chimini G., Kuiper J., Chapman M.J., Huby T., Van Berkel T.J.C., Van Eck M.
Coexistence of foam cells and hypocholesterolemia in mice lacking the ABC transporters A1 and G1.
Circ. Res., 2008;102:113-120.
*equally contributors

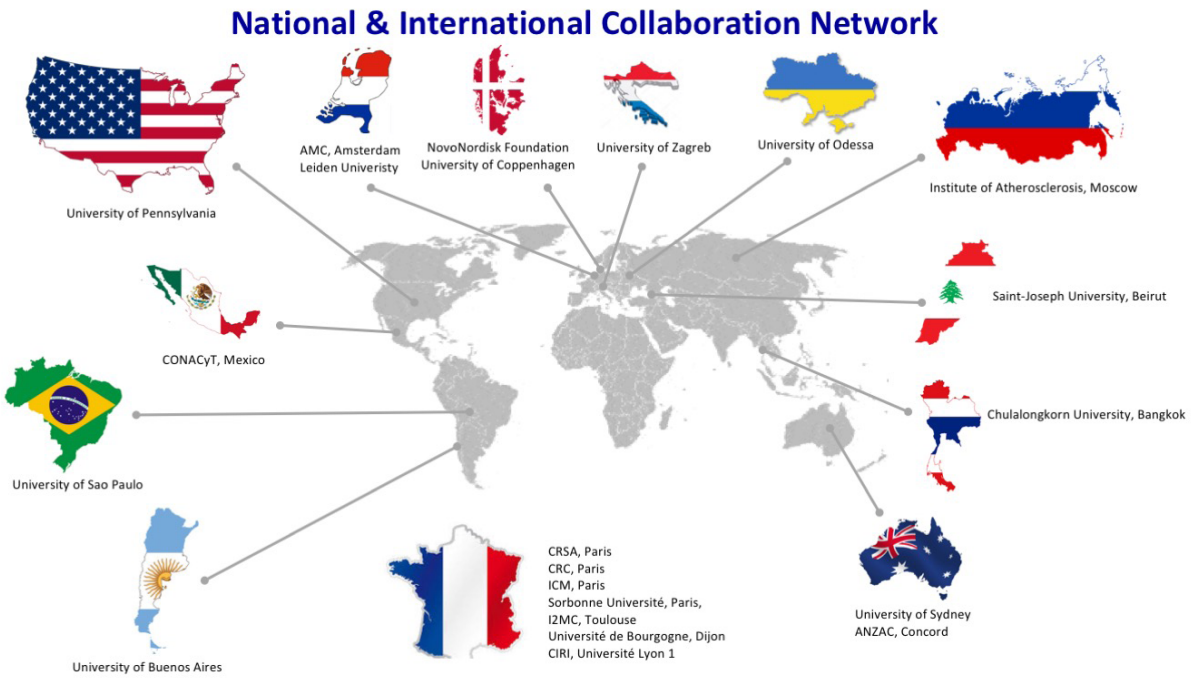
Silva RA, Huang R, Morris J, Fang J, Gracheva EO, Ren G, Kontush A, Jerome WG, Rye KA, Davidson WS.
Structure of apolipoprotein A-I in spherical high density lipoproteins of different sizes.
Proc. Natl. Acad. Sci. U S A. 2008;105(34):12176-81.

PATENTS

1. Transcription factor TF10 as a therapeutic agent and a biomarker (PCT/EP2018/073545).
2. Novel assay of HDL function. (EP17306042).
3. The ABCG1 gene as a marker and a target gene for treating obesity (PCT/EP2011/073140).
4. Reconstituted high density lipoprotein composition used e.g. for treating stroke, myocardial infarction, angina pectoris, pulmonary arterial hypertension and heart failure, comprises apolipoprotein and negatively charged phospholipid (EP2853259-A1).

FUNDS

COLLABORATIONS



KEYWORDS

HDL, cholesterol, triglycerid, lipid efflux, lipidomic, macrophage, biomarkers, cardiometabloc diseases

Team 5

MONONUCLEAR PHAGOCYTES IN CARDIOMETABOLIC DISEASES

>

THE TEAM

TEAM LEADER

Philippe LESNIK, *PhD, DR, Inserm*

INVESTIGATORS

Valérie CARREAU, *MD, PH, AP-HP*
Alice COILLARD, *PhD, Postdoc SU*
Philippe COUVERT, *MD, PhD, MCU-PH, SU*
Antonio GALLO, *MD, PH, AP-HP*
Emmanuel GAUTIER, *PhD, CR, Inserm*
Philippe GIRAL, *MD, PhD, Emeritus*
Xavier GIRERD, *MD, PhD, PU-PH, AP-HP*
Gérard HELFT, *MD, PhD, PU-PH, AP-HP*
Thierry HUBY, *PhD, CR, Inserm*
Pukar KC, *PhD, Postdoc, SU*

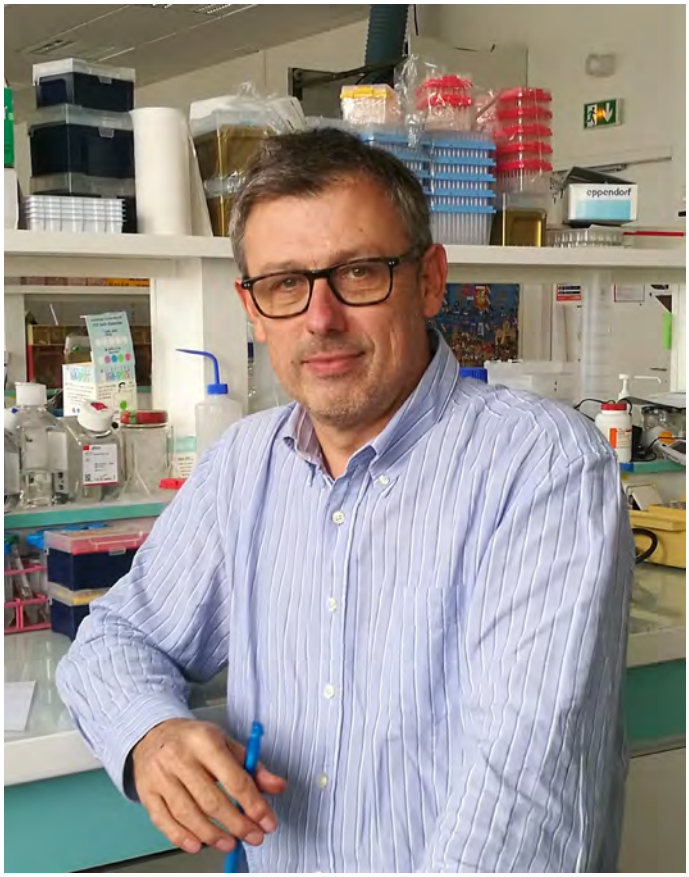
TECHNICAL ASSISTANTS

Sébastien DUSSAUD, *IE, Inserm*
Cheïma BENBIDA, *IE SU*

PHD STUDENTS

Rébecca FIMA
Marine BLANCHET
Caroline CHABAT COURREDE
Raoul MANUEL
Hua WANG

OBJECTIVES



Philippe Lesnik

The research team led by Philippe Lesnik is focused on the study of mononuclear phagocytes (MPs) in the context of cardiometabolic diseases. The team main objective is to better understand how different MPs subsets impact on chronic metabolic disorders, with particular emphasis on macrophages and dendritic cells. To this aim, unique mouse models and pre-clinical approaches will be used to decipher the complex interactions between MPs subsets and metabolic tissues. In addition, this team builds on recent cutting-edge preclinical and clinical proof-of-concepts evidencing a relationship between intestinal microbiota, immune cells and cholesterol metabolism in the host.

>

RESEARCH PROJECTS

THEME 1 - TOWARD A BETTER UNDERSTANDING OF MPS SUBSETS ROLES IN CHRONIC METABOLIC DISORDERS - E. GAUTIER

Mononuclear phagocytes (MPs) are a family of hematopoietic cells that comprise dendritic cells (DCs), monocytes as well as tissue-resident (rMac) and monocyte-derived inflammatory macrophages (iMac, arising during inflammatory insults). These cells are extremely diverse with regard to their origins, their phenotypes and behaviours (Gautier EL, Nat. Immunol 2012; Miller JC, Nat. Immunol 2012; Gautier & al. Blood 2013; Gautier EL & al. Immunol Rev 2014; Tussiwand R & al. Front Immunol 2015).
Over the past years, we have mainly focused on macrophage development and function in the steady state as well as macrophages role in acute inflammatory contexts. First, we have shed light (our own work as well as collaborative studies) on several key transcription factors controlling the development, maintainance or function of rMac in a tissue-specific manner (lung, peritoneum and brain) (Gautier EL and al. J. Immunol 2012, Gautier EL & al. J Exp Med 2014, Kim KW & al. J Exp Med 2016, Buttgereit A & al. Nat. Immunol 2016). These studies represent groundwork for further explorations aimed at specifying the roles played by rMac in their organ of residency during homeostasis and disease. Second, we explored several aspects of iMac biology in models of acute inflammation. In particular, we studied the molecular determinants of Ly-6C+ monocytes differentiation into iMac (Gautier EL & al. Blood 2013, Jakubzick C & al. Immunity 2013, Menezes S & al. Immunity 2016) and the mechanism by which iMac contracted during inflammation resolution (Gautier EL & al. Blood 2013, Calippe B & al Immunity 2017).
Scientific objectives. Overall, we want to pursue and extend the areas of research described above, and more specifically study the roles played by specific MPs subsets in the context of metabolic diseases. During metabolic disorders, lipid overload is usually central to the initiation of inflammatory reactions. Immune cells, and MPs in particular, could integrate and respond to these lipid-induced stresses, impacting on tissue functions. In addition, since MPs are not just sensors of the environmental changes, they could also regulate tissue homeostasis in a way it affects lipid homeostasis. Thus, there are many possible direct and indirect crosstalks between MPs (especially dendritic cells and macrophages) and key organs involved in metabolic homeostasis. We believe a better understanding of the division of labor among MPs subsets will be of interest in order to target and modulate specific MPs subsets functions to combat metabolic diseases.

Our objectives are :

- to better understand how rMac are maintained during metabolic diseases as well as the specific roles they play in disease. We will first focus on Kupffer cells and use mouse models allowing to specifically target this population.
- to test whether improving lysosomal-mediated lipid handling and catabolism in macrophages protects from the development of lipid overload-induced diseases.
- to understand how monocytes recruited to tissues get activated, differentiate into iMac and maintain themselves during acute and chronic inflammation.
- to understand how adipose tissue (AT) macrophages, and most specifically those recruited during states of energy imbalance (iMac), alter AT progenitors fate (adipogenic versus firbrogenic) to control AT remodelling and dysfunction in obesity.
- to determine if CD11b+ cDCs impacts on atherosclerosis as well as control the response to obesogenic diets.

Overall, we propose to assess how MPs subsets are regulated and how they impact on the tissue dysfunctions observed during metabolic disorders, with in mind to provide the proof-of-concept that targeting specific MPs activities can limit the pathology and its comorbidities. We will follow with the design of new approaches to allow for drug delivery to specific MPs subsets.

THEME 2 - MACROPHAGES, RED BLOOD CELLS AND CHOLESTEROL HOMEOSTASIS IN CARDIO-METABOLIC DISEASES - *T. HUBY*

Cholesterol is an essential component of vertebrate cell membranes. It is supplied by the diet or can be synthesized endogenously by all cells but red blood cells (RBCs). To maintain cholesterol balance, an amount of cholesterol equivalent to the sum of what is made in cells and acquired from the diet must be removed from the body. Reverse cholesterol transport (RCT), the process of removing excess cholesterol from peripheral tissues to the rapidly mixing plasma and tissue pool and then directing it to the intestine for excretion, has been an area of intense research because it bears the potential to reduce cardiovascular disease risk. The terminal portion of RCT involves 2 pathways: biliary secretion (via the liver) and an intestinal phase, named TICE (transintestinal cholesterol excretion) where cholesterol is both absorbed from the lumen and directly secreted into the lumen.

It is generally accepted that lipoproteins carry cholesterol in plasma. Yet, approximately half of whole blood volume is composed of RBCs and cholesterol concentration in RBCs is comparable to that found in plasma lipoproteins. Moreover, it has been recently shown that the RBC cholesterol pool can contribute to RCT (Hung &t al. ATVB 2012). Our studies have also demonstrated that invalidating one of the critical step of RCT- ie hepatic-SR-BI-mediated cholesterol uptake – leads to noticeable modifications in the RBC cholesterol pool and RBC blood concentrations (El Bouhassani & al. J Biol Chem 2011).

Erythrocytes maintain an intimate relationship with macrophages (Mac) from birth to death. Notably, Mac promotes erythrocyte development within erythroblastic islands in the bone marrow (BM) and senescent or damaged RBCs are phagocytosed by specialized Mac found primarily in the liver, spleen and bone marrow. Moreover, when there is an exceeding number of damaged RBC (i.e., in condition of hemolytic anemia), Mac in the liver contributes importantly to erythrocyte disposal and iron recycling, helping to prevent damage from uncontrolled iron and hemoglobin organ deposition (Theurl & al. Nat Med 2016).
Our team has contributed with others to reveal that modulation of the pool of tissue Mac in vivo resulted in important changes in cholesterolemia. More precisely, chemically-induced depletion of tissue Mac (i.e. clodronate liposome) or diminished Mac survival (with reduced Mac population) through transgenic approaches were associated with plasma cholesterol elevation (Shearn & al ATVB 2012; Bouchareychas and al. CVR 2015). Yet, the mechanisms or else the specific tissue Mac involved remain to be identified. Finally, our recent preliminary studies have demonstrated that dietary cholesterol has a strong impact on resident Mac of the liver and red pulp Mac of the spleen (RPM). This effect appeared to be tightly linked to enhanced erythrophagocytosis and affected liver iron store.

OBJECTIVE

Altogether, these findings and our preliminary results clearly indicate the existence of an intricate link between erythroid cells, tissue macrophages and cholesterol fluxes. Our objective is thus to now decipher the mechanistic pathways linking RBC and cholesterol metabolisms and the role played by macrophages in promoting and maintaining homeostasis in the context of cardio-metabolic diseases development.

Two aims are developed:

- **Aim 1.** To identify the contribution of specific tissue Mac to cholesterol homeostasis

Using newly developed mouse models by the team (E. Gautier), we will modulate specific tissue Mac populations and/or functions, primarily focusing on Kuppfer cells, to evaluate the impact on cholesterol homeostasis, including RCT via lipoproteins or RBC.

- **Aim 2.** To investigate the impact of dietary cholesterol on tissue macrophages and RBC, and highlight the potential pathophysiological consequences.

Building on our preliminary results, we will further explore in vivo how dietary cholesterol influences both RBC metabolism (erythropoiesis, phagocytosis, iron recycling) and tissue resident Mac populations (BM, kupffer cells, RPM, kidney and intestine Mac, etc.). Moreover, we will evaluate the pathophysiological implications of disturbed erythrophagocytosis on heme and iron tissue deposition, but also on Mac function/activation within metabolic tissues (liver, kidney, pancreas, etc.) and in atherosclerotic arterial lesions.

These studies should shed light on how macrophages control RBC and cholesterol metabolism interface. This project has the potential to reveal new mechanistic knowledge on how these metabolisms intercross to favor CMD development.

THEME 3 - TO DECIPHER FUNCTIONAL LINKS BETWEEN DENDRITIC CELLS GUT MICROBIOME AND CHOLESTEROL METABOLISM *- P. LESNIK*

Survival of dendritic cells (DCs) impacts cholesterol metabolism through crosstalk between liver gut and microbiome. In genetically manipulated mouse models in which DCs survival (CD11c-hBcl2 Tg; apoE-/-) (GM-CSF-/; apoE-/-) or functions (alteration of TGFb signalling in DC) were manipulated, we (Gautier et al. Circulation 2009) and other groups have reported unexpected changes in plasma cholesterol levels. However the mechanisms of such beneficial effects remain to be elucidated. Briefly, in the dyslipidemic CD11c-hBcl2 Tg model, we found that the reduction in plasma cholesterol levels is associated with changes in gut microbiota activity, which resulted in modification of cholesterol to coprostanol conversion, and of hydroxylation of secondary bile acids (BAs). Hence, this new metabolite milieu decreases intestinal cholesterol absorption and favors faecal sterol excretion due to changes in bile acids hydrophobicity. Our data also suggest that dendritic cells orchestrate metabolic responses through local adaptive immunity (sensing of gut microbiota), through mechanisms that involve gut barrier alterations (modulation of enterocytes, goblet cells functions) and regulatory immune mechanisms (Deswaerte V. et al manuscript under revision). We also demonstrate that DCs survival, has profound effects on intestinal microbiota composition and metabolic activities, thus affecting insulin sensitivity and adiposity (Lecuyer E et al. manuscript under revision) and that gut microbiota can impact significantly host cholesterol metabolism (Le Roy T et al. BMC Biol 2019). This is consistent with emerging data demonstrating that gut microbiota composition and functions are involved in the development of chronic immune and metabolic diseases such as obesity, diabetes, liver diseases and atherosclerosis. Moreover, statins, which are the first-line treatment for the prevention of CVD, display antimicrobial properties as well as pleiotropic properties on host cells (including immune cells), hence our aim is to characterize the microbial and immune contribution to therapeutic response. The efficacy of a treatment may largely vary between patients or models according not only to genetic but also to environemental factors. Identification of such factors is crucial to identify the mechanisms of the targeted disease and consequently to improve treatment efficacy and personalized medicine.

Hypothesis. Notably, we focus on the role of BAs that are cholesterol derivatives synthesized in the liver and then conjugated before secretion into the bile and small intestine. In the intestine, BAs control bacterial proliferation and overgrowth, whereas bacterial enzymes modify primary BAs through deconjugation, epimerization, dehydrogenation, dehydroxylation, and sulfation reactions to produce secondary BAs, which are reabsorbed for further processing and delivery of information to the host. Indeed, one attractive mechanism relies on a modulation of the functionality of bile acids by specific bacterial enzymes as BAs are now recognized as important signaling molecules with systemic endocrine functions. BAs are natural ligands for the nuclear receptor, farnesoid X receptor (FXR), and the plasma membrane-bound bile acid receptor TGR5. Through agonist or antagonist activities on these receptors bile acids regulate lipids and carbohydrate metabolism, energy homeostasis as well as immune responses. The global signaling capacity of BAs extends outside the gut-liver axis as suggested by expression BA-receptors in other key organs and cells including heart and immune cells.

OBJECTIVE

Collectively these results highlight reciprocal interactions of the gut microbiota and immune system that can impact cholesterol metabolism. Thus our objective is to further unravel the causal molecular mechanisms at work between host (via dendritic cells) and microbiota (via microbial metabolites [e.g. secondary BAs]).

For this purpose our objectives involve:

- **Aim 1**. to decipher the mechanisms of Bcl2 induced tolerogenic functions of dendritic cells in order to improve mucosal barrier integrity and endocrine functions of the microbiota. Transcriptomic analysis of DCs identifies candidate genes and gene sets in CD11c-hBcl2 mouse models, that will be further explored in vivo for their protective functions with a specific focus on the implication of secondary BAs.

- **Aim 2.** to reveal the causes of inter-individual variability of the effect of the hypocholesterolemic drugs statins through microbial-dependent and immune-dependent mechanisms in order to predict and optimize their efficacy and safety. Preliminary data obtained in avatar mice carrying specific microbial community from independent donors shows statin-specific responses and recipient-specific responses underlying pleiotropic but also beneficial/deleterious effects of statins as well as the variability in response to treatment.

Besides gaining mechanistic insight and identifying new pathways of improving gut barrier integrity, these projects should help to optimize use of therapeutic cholesterol-lowering drugs and to decipher how BAs may potentiate or on the contrary antagonize their therapeutic effects, notably in dyslipidemic experimental and clinical situations.

>

SELECTED PUBLICATIONS

Galle-Treger L, Moreau M, Ballaire R, Poupel L, Huby T, Sasso E, Troise F, Poti F, Lesnik P, Le Goff W, Gautier EL, Huby T.
Targeted invalidation of SR-B1 in macrophages reduces macrophage apoptosis and accelerates atherosclerosis.
Cardiovasc Res. 2019 May 22. pii: cvz138.

Guilbaud E, Gautier EL, Yvan-Charvet L.
Macrophage Origin, Metabolic Reprogramming and IL-1 Signaling: Promises and Pitfalls in Lung Cancer.
Cancers (Basel). 2019 Mar 2;11(3). pii: E298.

Pais R, Redheuil A, Cluzel P, Ratziu V, Giral P.
Relationship Among Fatty Liver, Specific and Multiple-Site Atherosclerosis, and 10-Year Framingham Score.
Hepatology. 2019 Apr;69(4):1453-1463.

Giral P, Neumann A, Weill A, Coste J.
Cardiovascular effect of discontinuing statins for primary prevention at the age of 75 years: a nationwide population-based cohort study in France.
Eur Heart J. 2019 Nov 14;40(43):3516-3525.

Rosenbaum D, Gallo A, Lethielleux G, Bruckert E, Levy BI, Tanguy ML, Dulon J, Dahmoune N, Salem JE, Bittar R, Leban M, Girerd X, Touraine P, Bachelot A; CARDIOHCS study group.
Early central blood pressure elevation in adult patients with 21-hydroxylase deficiency.
J Hypertens. 2019 Jan;37(1):175-181.

Tiphaine Le Roy, Emelyne Lécuyer, Benoit Chassaing, Moez Rhimi, Marie Lhomme, Samira Boudebbouze, Farid Ichou, Júlia Haro Barceló, Thierry Huby, Maryse Guerin, Philippe Giral, Emmanuelle Maguin, Nathalie Kapel, Philippe Gérard, Karine Clément & Philippe Lesnik
The intestinal microbiota regulates host cholesterol homeostasis
BMC Biology volume 17, Article number: 94 (2019)

Sharma A, Agrawal S, Garg A, Vallakati A, Lavie CJ, Helft G.
Duration of dual antiplatelet therapy following drug-eluting stent implantation: A systemic review and meta-analysis of randomized controlled trials with longer follow up.
Catheter Cardiovasc Interv. 2017 Jul;90(1):31-37.

Helft G.
New guidelines on duration of dual antiplatelet therapy in patients with coronary artery disease: what's the novelty?
J Thorac Dis. 2016 Oct;8(10).

Helft G, Steg PG, Le Feuvre C, Georges JL, Carrie D, Dreyfus X, Furber A, Leclercq F, Eltchaninoff H, Falquier JF, Henry P, Cattan S, Sebagh L, Michel PL, Tuambilangana A, Hammoudi N, Boccara F, Cayla G, Douard H, Diallo A, Berman E, Komajda M, Metzger JP, Vicaut E;
OPTImal DUAL Antiplatelet Therapy Trial Investigators. Stopping or continuing clopidogrel 12 months after drug-eluting stent placement: the OPTIDUAL randomized trial.
Eur Heart J. 2016;37(4):365-74.

Petroni T, Zaman A, Georges JL, Hammoudi N, Berman E, Segev A, Juliard JM, Barthelemy O, Silvain J, Choussat R, Le Feuvre C, Helft G.
Primary percutaneous coronary intervention for ST elevation myocardial infarction in nonagenarians.
Heart 2016;102:1648-54.

Helft G, Georges JL, Mouranche X, Loyeau A, Spaulding C, Caussin C, Benamer H, Garot P, Livarek B, Teiger E, Varenne O, Monségu J, Mapouata M, Petroni T, Hammoudi N, Lambert Y, Dupas F, Laborne F, Lapostolle F, Lefort H, Juliard JM, Letarnec JY, Lamhaut L, Lebail G, Boche T, Jouven X, Bataille S; e-MUST and CARDIO-ARSIF Registries.
Outcomes of primary percutaneous coronary interventions in nonagenarians with acute myocardial infarction.
Int J Cardiol. 2015; 192:24-9.

Veglia F, Baldassarre D, de Faire U, Kurl S, Smit AJ, Rauramaa R, Giral P, Amato M, Di Minno A, Ravani A, Frigerio B, Castelnuovo S, Sansaro D, Coggi D, Bonomi A, Tedesco CC, Mannarino E, Humphries SE, Hamsten A, Tremoli E; IMPROVE study group.
A priori-defined Mediterranean-like dietary pattern predicts cardiovascular events better in north Europe than in Mediterranean countries.
Int J Cardiol. 2019 May 1;282:88-92.

Franceschini N, Giambartolomei C, de Vries PS, Finan C, Bis JC, Huntley RP,Lovering RC, Tajuddin SM, Winkler TW, Graff M, Kavousi M, Dale C, Smith AV, Hofer E, van Leeuwen EM, Nolte IM, Lu L, Scholz M, Sargurupremraj M, Pitkänen N, Franzén O, Joshi PK, Noordam R, Marioni RE, Hwang SJ, Musani SK, Schminke U, Palmas W, Isaacs A, Correa A, Zonderman AB, Hofman A, Teumer A, Cox AJ, Uitterlinden AG, Wong A, Smit AJ, Newman AB, Britton A, Ruusalepp A, Sennblad B, Hedblad B, Pasaniuc B, Penninx BW, Langefeld CD, Wassel CL, Tzourio C, Fava C, Baldassarre D, O'Leary DH, Teupser D, Kuh D, Tremoli E, Mannarino E, Grossi E, Boerwinkle E, Schadt EE, Ingelsson E, Veglia F, Rivadeneira F, Beutner F, Chauhan G, Heiss G, Snieder H, Campbell H, Völzke H, Markus HS, Deary IJ, Jukema JW, de Graaf J, Price J, Pott J, Hopewell JC, Liang J, Thiery J, Engmann J, Gertow K, Rice K, Taylor KD, Dhana K, Kiemeney LALM, Lind L, Raffield LM, Launer LJ, Holdt LM, Dörr M, Dichgans M, Traylor M, Sitzer M, Kumari M, Kivimaki M, Nalls MA, Melander O, Raitakari O, Franco OH, Rueda-Ochoa OL, Roussos P, Whincup PH, Amouyel P, Giral P, and al.
GWAS and colocalization analyses implicate carotid intima-media thickness and carotid plaque loci in cardiovascular outcomes.
Nat Commun. 2018 Dec 3;9(1):5141.

El Khoury P, Couvert P, Elbitar S, Ghaleb Y, Abou-Khalil Y, Azar Y, Ayoub C, Superville A, Guérin M, Rabès JP, Varret M, Boileau C, Jambart S, Giral P, Carrié A, Le Goff W, Abifadel M.
Identification of the first Tangier disease patient in Lebanon carrying a new pathogenic variant in ABCA1.
J Clin Lipidol. 2018 Nov - Dec;12(6):1374-1382.

Pais R, Redheuil A, Cluzel P, Ratziu V, Giral P. Relationship Among Fatty Liver,
Specific and Multiple-Site Atherosclerosis, and 10-Year Framingham Score.
Hepatology. 2019 Apr;69(4):1453-1463.

Giral P.
Comparison of Five Major Guidelines for Statin Use in Primary Prevention.
Ann Intern Med. 2018 Jul 3;169(1):67.

Rosenbaum D, Gallo A, Lethielleux G, Bruckert E, Levy BI, Tanguy ML, Dulon J, Dahmoune N, Salem JE, Bittar R, Leban M, Girerd X, Touraine P, Bachelot A; CARDIOHCS study group.
Early central blood pressure elevation in adult patients with 21-hydroxylase deficiency.
J Hypertens. 2019 Jan;37(1):175-181.

Gallo A, Rosenbaum D, Kanagasabapathy C, Girerd X.
Effects of carotid baroreceptor stimulation on retinal arteriole remodeling evaluated with adaptive optics camera in resistant hypertensive patients.
Ann Cardiol Angeiol (Paris). 2017 Jun;66(3):165-170.

Rosenbaum D, Mattina A, Koch E, Rossant F, Gallo A, Kachenoura N, Paques M, Redheuil A, Girerd X.
Effects of age, blood pressure and antihypertensive treatments on retinal arterioles remodeling assessed by adaptive optics.
J Hypertens. 2016 Jun;34(6):1115-22

Lefort M, Neufcourt L, Pannier B, Vaïsse B, Bayat S, Grimaud O, Girerd X.
Sex differences in adherence to antihypertensive treatment in patients aged above 55: The French League Against Hypertension Survey (FLAHS).
J Clin Hypertens (Greenwich). 2018 Oct; 20(10):1496-1503.

Hansel B, Roussel R, Giral P.
Associations of fats and carbohydrates with cardiovascular disease and mortality-PURE and simple?
Lancet. 2018 Apr 28;391(10131):1680.

Szalat R, Pirault J, Fermand JP, Carrié A, Saint-Charles F, Olivier M, Robillard P, Frisdal E, Villard EF, Cathébras P, Bruckert E, Chapman MJ, Giral P, Guerin M, Lesnik P, Le Goff W.
Physiopathology of necrobiotic xanthogranuloma with monoclonal gammopathy.
J Intern Med. 2014 Sep;276(3):269-84

>

Gilibert S, Galle-Treger L, Moreau M, Saint-Charles F, Costa S, Ballaire R, Couvert P, Carrié A, Lesnik P, Huby T.
Adrenocortical scavenger receptor class B type I deficiency exacerbates endotoxic shock and precipitates sepsis-induced mortality in mice.
J Immunol. 2014 Jul 15;193(2):817-26

Bouchareychas L, Pirault J, Saint-Charles F, Deswaerte V, Le Roy T, Jessup W, Giral P, Le Goff W, Huby T, Gautier EL and Lesnik P.
Promoting macrophage survival delays progression of pre-existing atherosclerotic lesions through macrophage-derived apoE.
Cardiovasc Res. 2015;108:111-23

Beliard S, Le Goff W, Saint-Charles F, Poupel L, Deswaerte V, Boucharechas L, Huby T, Lesnik P.
Modulation of Gr1low monocytes subset impacts insulin-sensitivity and weight gain upon high-fat diet in female mice.
Int J Obes (Lond). 2017 Sep. 10.1038.

Guerin M, Silvain J, Gall J, Darabi M, Berthet M, Frisdal E, Hauguel-Moreau M, Zeitouni M, Kerneis M, Lattuca B, Brugier D, Collet JP, Lesnik P, Montalescot G.
Association of Serum Cholesterol Efflux Capacity With Mortality in Patients With ST-Segment Elevation Myocardial Infarction.
J Am Coll Cardiol. 2018 Dec 25;72(25):3259-3269.

El Khoury P, Waldmann E, Huby T, Gall J, Couvert P, Lacorte JM, Chapman J, Frisdal E, Lesnik P, Parhofer KG, Le Goff W, Guerin M.
Extended-Release Niacin/Laropiprant Improves Overall Efficacy of Postprandial Reverse Cholesterol Transport.
Arterioscler Thromb Vasc Biol. 2016 Feb;36(2):285-94.

Frisdal E, Le Lay S, Hooton H, Poupel L, Olivier M, Alili R, Plengpanich W, Villard EF, Gilibert S, Lhomme M, Superville A, Miftah-Alkhair L, Chapman MJ, Dallinga-Thie GM, Venteclef N, Poitou C, Tordjman J, Lesnik P, Kontush A, Huby T, Dugail I, Clement K, Guerin M, Le Goff W.
Adipocyte ATP-binding cassette G1 promotes triglyceride storage, fat mass growth, and human obesity.
Diabetes. 2015 Mar;64(3):840-55.

Westerterp M, Gautier EL, Ganda A, Molusky MM, Wang W, Fotakis P, Wang N, Randolph GJ, D'Agati VD, Yvan-Charvet L, Tall AR.
Cholesterol Accumulation in Dendritic Cells Links the Inflammasome to Acquired Immunity.
Cell Metab. 2017 Jun 6;25(6):1294-1304.

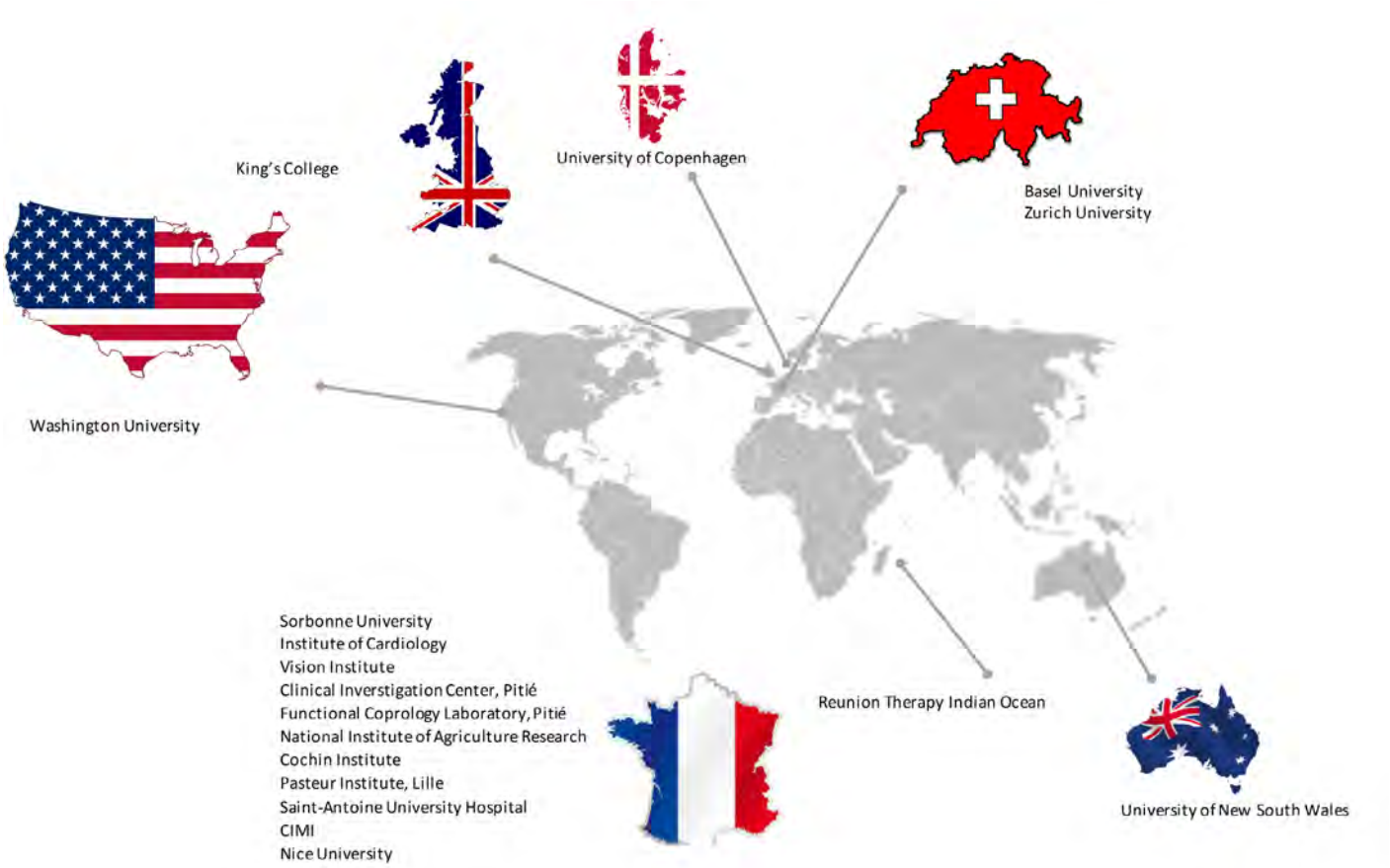
Calippe B, Augustin S, Beguier F, Charles-Messance H, Poupel L, Conart JB, Hu SJ, Lavalette S, Fauvet A, Rayes J, Levy O, Raoul W, Fitting C, Denèfle T, Pickering MC, Harris C, Jorieux S, Sullivan PM, Sahel JA, Karoyan P, Sapieha P, Guillonneau X, Gautier EL, Sennlaub F.
Complement Factor H Inhibits CD47-Mediated Resolution of Inflammation.
Immunity. 2017 Feb 21;46(2):261-272.

Marcelin G, Ferreira A, Liu Y, Atlan M, Aron-Wisnewsky J, Pelloux V, Botbol Y, Ambrosini M, Fradet M, Rouault C, Hénégar C, Hulot JS, Poitou C, Torcivia A, Nail-Barthelemy R, Bichet JC, Gautier EL, Clément K.
A PDGFRα-Mediated Switch toward CD9high Adipocyte Progenitors Controls Obesity-Induced Adipose Tissue Fibrosis
Cell Metab. 2017 Mar 7;25(3):673-685.

Sarrazy V, Sore S, Viaud M, Rignol G, Westerterp M, Ceppo F, Tanti JF, Guinamard R, Gautier EL, Yvan-Charvet L.
Maintenance of Macrophage Redox Status by ChREBP Limits Inflammation and Apoptosis and Protects against Advanced Atherosclerotic Lesion Formation.
Cell Rep. 2015 Oct 6;13(1):132-144.

Kim KW, Williams JW, Wang YT, Ivanov S, Gilfillan S, Colonna M, Virgin HW, Gautier EL, Randolph GJ.
MHC II+ resident peritoneal and pleural macrophages rely on IRF4 for development from circulating monocytes.
J Exp Med. 2016 Sep 19;213(10):1951-9.

COLLABORATIONS



FUNDS

Agence Nationale de la Recherche ANR

Fondation de France

Fédération Française de Cardiologie

PARIS

BIOLOGICAL RESOURCES

Experimental models of atherosclerosis and cardiometabolic diseases
Genetically-modified mice (tg CD68-hBCL2, CD11c-hBcl2, SR-BI flox/flox)

BIOLOGICAL RESOURCES - METHODOLOGIES USED

Expertise in lipoprotein metabolism, atherosclerosis and mononuclear phagocytes.
Development of mouse models for cardiometabolic diseases.
Metabolic phenotyping of mouse models.
Transcriptomic, Lipidomic, Metabolomic, Metagenomic, Epigenomic, Multivariate analysis.
Phenotyping and quantification of circulating and tissue leucocytes: flow cytometry/cell sorting.
Reverse cholesterol transport in vivo and in vitro.
Axenic mice, faecal material transfer.

KEYWORDS

Atherosclerosis, Lipoproteins, Lipids, Lipid sensors/receptors, Inflammation, Immunity, Mononuclear cells, Macrophages, Dendritic cells, Kupffer cells, Apoptosis, Genetic/Epigenetic, Microbiota.

Administration

ADMINISTRATIVE AND FINANCIAL OFFICE

GENERAL SECRETARY

- Estelle MENDES

The Managing Director oversees the administrative and financial Office. She is in charge of implementing the decisions of the Director and Team Leader Board. She ensures full support from the administration for research activities.

FINANCIAL RESOURCES

- Estelle MENDES

As the Finance Officer, Estelle Mendes prepares and organizes the budget of the unit. She is in charge of the management of all the resources of the lab, i.e. Inserm and Sorbonne Université allocations and external funds. She ensures the management of the accounting and financial management in connection with the principal investigators, the Inserm regional Delegation and Sorbonne University-School of Medicine financial Department.

She ensures the coordination of the financial assistants who are in charge of the daily financial activities:

- Roberte LE GALLEU
- Angélique RIQUELME

HUMAN RESOURCES

- Nathalie ABIOLA

Nathalie Abiola is in charge of the Human Resources domain and manages all the activities relative to the civil and the temporary staff in the lab, following the good practices and the regulatory guidelines of Inserm and Sorbonne University.

She manages a large set of activities : from the administrative preparation of the recruitments to the reception of the new arrivals. She follows up the events in the agent career. She ensures the development of the skills through training and forward planning.

Nathalie Abiola is an expert in the Humain Resources domain and offers decision-making tools to the head of the unit as well as to the team leaders, realising studies and analyses. She also coordinates the national campains of new positions and promotions of our guardianship institutions.

COMMUNICATION

- Martine DUQUESNE

She implements the policy of internal and external communication. She edits the unit newsletter, *La Lettre interne*, and is, with Nathalie Neyroud, Team 1 researcher, administrator of the website.

She collaborates in editing documents of the unit presentation, as well as the report for HCERES evaluation or the unit presentation booklets.
She is the referent of Inserm and Sorbonne University-School of Medicine communication departments in the unit and makes the connection between the two institutions and the unit researchers concerning scientific mediation. She is a member of Inserm Journal *In Vivo* editorial committee.

CENTRAL WAREHOUSE AND WASHING ROOM FACILITIES

- Claire PERRET

Claire Perret is responsible of the warehouse and manages the washing software. Eric Frisdal manages the washing service.

Operators:

- Mourad OUCHENE
- Rabah JELLOUL

Mourad Ouchene, coordinator, takes care of the washing service, the inventory of the warehouse and the supplied consumable products with Rabha Jelloul's assistance.

FACILITES

Radioactive activities

Eric FRISDAL and Hervé DURAND, competent persons in radiation protection.

Our laboratory is authorised by the Nuclear Safety Authority (ASN) in order to hold and to use different radionucleides as ^{3}H (450 MBq), ^{14}C (37 MBq), ^{32}P (185 MBq) and ^{35}S (185 MBq), authorisation number T751168.

RISK PREVENTION

- Hervé DURAND

Referents on risk prévention :

- Fabrice ATASSI
- Sophie GALIER

They assist and advise the Director, the Administrative Manager and the team leaders in the implementation of the safety regulations and occupational health. They work with the Inserm Head of prevention. They ensure the implementation of good practices of research in the laboratory.

ACKNOWLEDGEMENTS

Photographic credits

Hubert Grillot, UMRS 1166, cover photo
Pascal Tournaire, IHU-ICAN, p. 9
Pierre Kitmacher, SU, p. 13
Catherine Pavoine, UMRS 1166, p. 43
Martine Duquesne, UMRS 1166, p. 59
Wilfried Le Goff, UMRS 1166, p. 75

Conception and Graphism

Laurence Jacquenod, Graphist, Communication
Department School of Medicine Sorbonne
University

Conception and Editing

Martine Duquesne, in Charge of Communication,
UMRS 1166

2019
2020

Research unit on cardiovascular and metabolic diseases