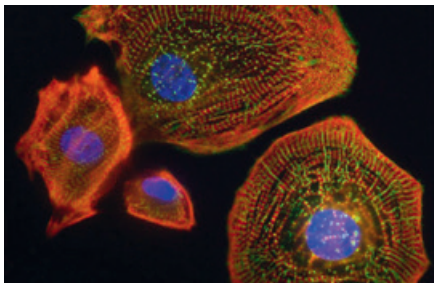
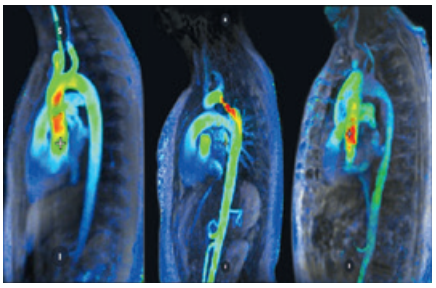
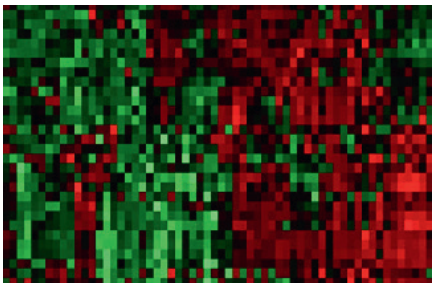
ACTIVITY REPORT
2018 / 2020

CHRONIC CARDIOMETABOLIC DISEASES

INVENTING
TOMORROW'S
MEDICINE

ICAN Institute of Cardiometabolism And Nutrition

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PR. STÉPHANE HATEM

MESSAGE FROM THE CHIEF EXECUTIVE

Cardiovascular diseases linked to diabetes, atherosclerosis, obesity and liver diseases such as NASH, are increasing rapidly in France as in all economically-developed countries; they are now grouped under the concept of cardiometabolic diseases. There are scientific bases for this concept, made up of the numerous interfaces between metabolism and organs: microbiota, adipose tissue, and the immune system. There has therefore been a shift away from organ-centered medicine towards a global and systemic approach to cardiometabolic diseases. Technological progress, in particular medical imaging, and advances in scientific knowledge, have made it possible to study these interfaces and enabled this integrative and systemic vision. Medical imaging enables the study of these interfaces. Following static anatomy and the physiology of an organ, imaging is capable of seeing - with increasing definition - the composition and biology of tissues, such as their metabolic profile and oxidative stress.
The expansion of OMICs, notably metabolomics and the progression in the analysis of big data applied to medicine, have contributed widely to a systemic and multidisciplinary approach to combat these diseases. For research, this has meant a change of scale. For medicine, it has created a need to reinvent treatment plans and develop tools for precision medicine for metabolic diseases.

The HUI-ICAN [Hospital-University Institute - Institute of Cardiometabolism and Nutrition] was created to respond to these challenges. Embedded within a unique ecosystem of research units and medical departments dedicated to cardiometabolic diseases, HUI-ICAN represent a community of 400 doctors and researchers from the AP-HP [Public Assistance - Hospitals of Paris], INSERM [National Institute of Health and Medical Research] and the Sorbonne-Université [Sorbonne University], it is structured around three pillars: state-of-the-art research platforms, operational units for setting up projects and public/private partnerships, and a public research foundation that allows for responsiveness and agility. The HUI-ICAN has been a pioneer in the study of the relationship between the microbiota of the intestinal flora and cardiometabolic diseases, in the discovery of fatty tissue around the heart plays a role in the onset of arrhythmias, and in the interaction between liver disease and atherosclerosis. The teams that run the HUI-ICAN are positioned throughout the lifetime of cardiometabolic diseases, from parents' imprint on the fœtus, the journey from adolescence to adulthood, to the acute episodes that too often reveal the progression of cardiometabolic diseases. Several patient treatment plans have been set up for comprehensive management; for example, from the diagnosis of steatosis of the liver (NASH) to its impact on the progression of arterial atherosclerosis. The HUI teams are creating new algorithms that enable clinical imaging to see beyond the structure of an organ. These algorithms are then validated on patients thanks to a unique imaging platform in Ile-de-France dedicated to human research. Thanks to its organisation, its research resources and its community, HUI is fully mobilised to advance the knowledge of cardiometabolic diseases and accelerate the advent of precision medicine for the benefit of patients.

Three pillars: state-of-the-art research platforms, operational units for setting up projects and public/private partnerships, and a public research foundation that enables responsiveness and agility.

THE HUI-ICAN
10 YEARS OF INNOVATION

RESEARCH

5 167
ARTICLES PUBLISHED
of which 270 were in the top 1% of most-cited articles

186 ***ARTICLES OF CONSENSUS AND INTERNATIONAL RECOMMENDATIONS***

8
CUTTING-EDGE TECHNOLOGY PLATFORMS

12 ***TEAMS RESEARCH***

1 ***MRI***
dedicated to human research and imaging (sole platform in Ile-de-France)

TREATMENTS

168
DOCTORS

4 ***TREATMENT PLANS***
innovative

42 572
PATIENTS
included in registers, cohorts or clinical trials

6 ***CENTRES***
rare diseases referrals

1 ***PLATFORM FOR CLINICAL RESEARCH***
specialised in cardiometabolism and nutrition diseases

PARTNERSHIPS

9.5 m€
IN MANUFACTURING
financing

29
PATENTS FILED

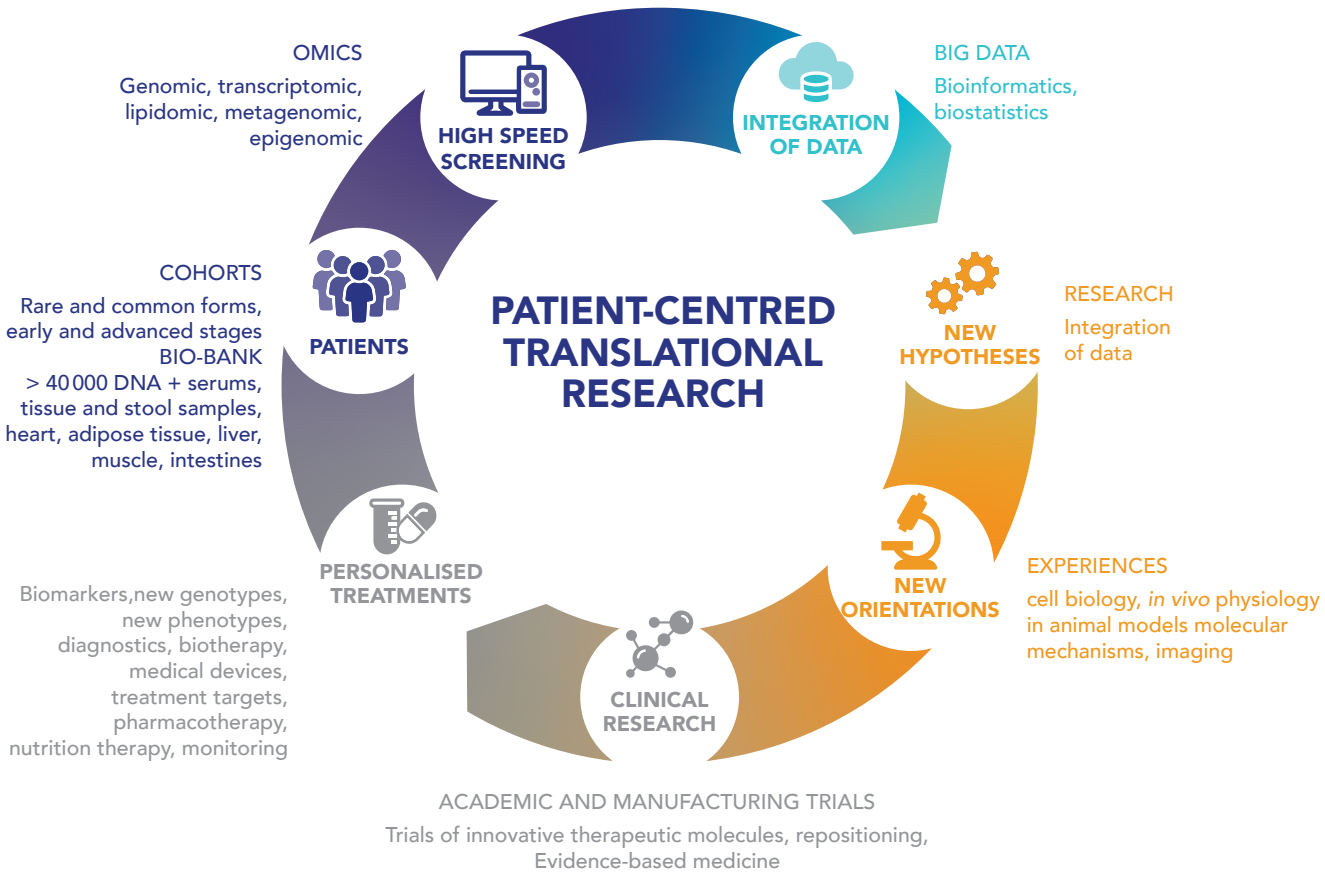
28
LARGE-SCALE PARTNERSHIP PROJECTS

36.8 m€
IN MANUFACTURING
from calls for tender

HUI
A UNIQUE EXAMPLE

2019 marked a key stage in the HUI-ICAN's journey with the renewal of its "Hospital-University Institute" denomination. The ICAN is a hub of scientific and medical excellence, its mission is to accelerate progress in research to invent the medicines of tomorrow, future treatments and new practices in cardiometabolism and nutrition.
The HUI-ICAN is a Scientific Cooperation Foundation whose three founding members are: Assistance Publique - Hôpitaux de Paris (Executive Director Martin HIRSCH), Sorbonne University (President Jean CHAMBAZ), the National Institute of Health and Medical Research (President and Executive Director GillesBLOCH).
In collaboration with the ICAN, they define the trajectory of the HUI.

HUI
A UNIQUE EXAMPLE



To speed up the fight against cardiometabolic diseases, the HUI-ICAN is working to translate scientific discoveries into concrete clinical applications for patients. ICAN's strength is that it brings together the best clinical experts in cardiometabolic and nutritional diseases and high-level research teams, to develop innovative research programmes. The ICAN integrates foundational research, translational research and clinical research activities. This research continuum relies on ICAN's technology platforms and on a network of internationally renowned clinicians to accelerate innovation: biomarker discoveries, evaluation of innovative drugs, new therapies or new medical devices for patients with cardiometabolic and nutritional diseases.

GOVERNANCE

The HUI is led by a **board of trustees** (BT) that sets overall policies. It is composed of 16 members: 6 founding members, 5 qualified persons, 3 representatives from the financial world and 2 representatives elected by the research teachers. The BT is chaired by Mr Thierry Tutot, a Councillor of State.

The chief executive, chosen among a group of candidates proposed by the BT, is appointed for 4 years by the President of the board of trustees. The chief executive oversees the general management of the HUI and are upported by a General Secretary, who is responsible for the operational management of the Institute.

The HUI's executive committee (COMEX) is comprise of the chief executive,the general secretary, the heads of the HUI's internal divisions and one community representative per strategic axis. The Director of the Groupe Hospitalier de la Pitié-Salpêtrière [Pitié-Salpêtrière Hospital Group] and the Medical Director of the MUD are permanent invitees. COMEX is tasked with helping the chief executive, not only in defining the HUI's strategy and scientific orientation, but also with all other managerial aspects.

The HUI Board is composed of the HUI Executive Director; the General Secretary; the Dean of Sorbonne University, Faculty of Medicine; the directors and team leaders of the JRU teams involved with the ICAN; the Medical Director of the DMU Archimede [Archimedes Medical-University Department]; and the department heads of this MUD involved in the ICAN's clinical activities. The chair of the HUI's board is the HUI's chief executive. Its objective is to strengthen internal cohesion of the HUI's medical and scientific community and to allow a flow of information between the teams to ensure overall consistency.
The purpose of the HUI board is to enable an exchange and the sharing of the strategic orientations and scientific policy of the HUI.

STEERING COMMITTEES

DECISION MAKING

STEERING COMMITTEES

International Scientific Council

Board of Trustees

President
Mister
Thierry TUOT

Coordination Committee with the Founders

Remuneration Committee

HUI Board

Chief Executive
Professor
Stéphane HATEM

Executive Committee

Development Committee

General Secretary
Missus
Anne LESTIENNE

Scientific operations
Stéphane COMMANS

Scientific platforms
Ludovic LE CHAT

Clinical research platform
Recruitment in progress

Legal and development
Maud DECRAENE

Administration and finance
Stéphanie LAPOUS

Communication and sponsorship
(2021)
Francine TROCMÉ

MESSAGE
FROM THE CHIEF EXECUTIVE

Anne Lestienne
took up her role
as General Secretary
of the HUI-ICAN
on the 2nd January 2019.

The period 2018-2020 was marked by an in-depth review of the strategic positioning of the HUI and its missions. I joined ICAN in 2019 to assist with this restructuring. All the teams, both scientific and in support functions, have mobilised to give new impetus to the HUI-ICAN and to redefine an ambitious trajectory congruent with the excellence of its community of researchers and doctors and the public health challenges represented by cardiometabolic diseases in France, and also in all developed-economy countries.

The ICAN, in consultation with its founders, has thus chosen to refocus on its role as a hub by becoming an indispensable bridge between its scientific and medical community and the industrial players: assistance in setting up projects, regulatory safety, short circuits, and the expertise of the of technology platforms are essential strengths for bringing ICAN's missions to fruition.

The ICAN, together with its founders, has therefore chosen to refocus on its role as a hub.

We were able to reinvent the platforms to align them more closely to the needs of the researchers. In addition, three priority areas have been identified and are now the driving force behind numerous projects: the MRI, the cohort plan and the offer to companies to boost partnership research in the cardiometabolic sector. These in-depth transformations, which the partners have been able to effect, have led to some great successes, such as obtaining European H2020 funding for the Maestria project: Machine Learning Artificial Intelligence Early Detection Stroke Atrial. *The HUI project update was also accompanied by an update of the multi-year financial trajectory, in order to integrate the changes and to translate them into concrete budgetary terms. The aim is to become more efficient and to operate in full accordance with an updated strategic project and economic trajectory. I am delighted to have contributed to these large-scale developments alongside the HUI-ICAN community to build, together, tomorrow's treatments for cardiometabolic diseases.*

THE BOARD OF ADMINISTRATION 2020

Thierry TUOT
President of the Board of Trustees
Counsellor of State

Martin HIRSCH
Executive Director, AP-HP
Founder

Gilles BLOCH
President and executive director of INSERM
Founder

Jean CHAMBAZ
President of Sorbonne University
Founder

Elli CHATZOPOULOU
Director of partnerships and external relations, INSERM
Founder

Marc HUMBERT
PU-PH AP-HP
Founder

Bruno RIOU
Dean of the Faculty of Medicine Sorbonne University
Founder

Catherine BOILEAU
PU-PH AP-HP
Qualified person

Claudine CANALE
President,
Les Poids Plume Association
Qualified person

Stanislav DUSKO EHRLICH
Director of research INRA
Qualified person

Bruno FEVE
Director of the Research Unit and Centre and team leader - CRSA - JRU 5938
Representative, research teachers

Philip JANIAK
Director of cardiovascular research SANOFI
Economic world

Stéphane ROQUES
CEO - MEDICEN
Qualified person

Pierre SONIGO
Director, R&D and medical commerce
Economic world

THIERRY TUOT
PRESIDENT OF THE BOARD OF TRUSTEES

As with all start-ups, ICAN may have raised doubts about the viability of its future. The retrospective look at its growth that this report allows, shows that the future of our HUI is now firmly assured and that its project is unfolding with vigour. These past two years have been ones of standardisation, of management that has become rigorous, transparent and efficient; of consolidation, by refocusing the institute on its fundamentals; of investment, with the acquisition of the research MRI, unique in its genre, which is our master asset; of integration, as ICAN has, working closely together with its founders in permanent collaboration, found its direction, its specificity, and the pathway of its added-value. Despite the health crisis (to which it is contributing to its future resolution), the HUI has remained mobilised and active; it has demonstrated that its project is valid, and has found reliable partners in France and Europe, with whom it is writing, as a recognised major player, an essential chapter in medical research. It owes its accomplishments to the unfailing support - which is not a gamble, but a rational choice for the future - of its founding members, Sorbonne University, AP-HP and INSERM. It owes its success, first and foremost, to its dedicated teams; united, energised, professional and imaginative, whose creativity and rigour have rendered the tool that they built so powerful. The Board of Trustees will continue alongside them, to support and promote action whose value will be further demonstrated in the years to come.

SCIENTIFIC ADVISORY BOARD

The ICAN's scientific council is composed of 5 external members in the fields of cardiometabolism and nutrition, all of whom are highly recommended by the international scientific community. This scientific governance body, designated by the Board of Trustees, is consulted on the HUI's major scientific orientations and annual action programme. The scientific council also evaluates the Foundation's scientific performance. It is very engaged in the scientific life of the ICAN and plays a fundamental role.

Pr. Rozemarijn VLIEGENTHART
the Netherlands

Pr. Martin BENNETT
United Kingdom

Pr. Stéphan HERZIG
Germany

Dr David SAVAGE
United Kingdom

Pr. Arnold VON ECKARDSTEIN
Switzerland

ROZEMARIJN VLIEGENTHART

CARDIO-THORACIC RADIOLOGIST - UNIVERSITY OF GRONINGEN - THE NETHERLANDS

ICAN is a unique research institute due to its multidisciplinary approach to a central and complex morbidity problem, cardiometabolic diseases, and broad research scope, from basic research to implementation, using state-of-the-art techniques. A particular strength of this world-wide leading institute is the involvement of experts from different fields, including clinic, -omics and imaging, in research projects, leading to new insights on pathophysiology, biomarkers and potential targets for treatment or response evaluation. Importantly, ICAN has a central focus on the patient and their journey, and prevention. Lastly, I think a key component that helps to anchor the research findings and techniques is the ICAN education and teaching programme for future colleagues in research and clinic.

FROM **RESEARCH** TO **TREATMENT**

THE SPHERES OF ACTIVITY OF THE HUI-ICAN 2020

THE CLINICAL TEAMS

ARCHIMEDE MEDICAL-UNIVERSITY DEPARTMENT (MUD)

Led by Pr. Richard ISNARD

The ARCHIMEDES MUD brings together the departments and units involved in the care and treatment of acute and chronic cardiovascular and metabolic diseases, as well as certain rare pathologies of the Sorbonne University Hospital Group. The DMU's involvement meets an objective of coherence of care in these pathologies across eastern Paris, and to improvement the treatment plans within teams that have a long history of collaboration between themselves, and a strong local, national and international visibility.

Pitié-Salpêtrière Hospital Group

INSTITUTE OF CARDIOLOGY

- Cardiology department
  Pr. Gilles MONTALESCOT
- Cardiovascular and thoracic surgery department Pr. Pascal LEPRINCE
- Department of intensive care medicine
  Pr. Alain COMBES
- Vascular surgery department
  Pr. Laurent CHICHE

INSTITUT E3M [E3M INSTITUTE]

- Diabetes department
  Pr. Agnès HARTMANN
- Endocrinology and reproductive medicine department Pr. Philippe TOURAINE
- Endocrinology, Metabolism and Prevention of Cardiovascular diseases department
  Pr. Eric BRUCKERT
- Functional unit for thyroid pathologies and endocrine tumours
  Pr. Laurence LEENHARDT
- Internal medicine department
  Pr. Zahir AMOURA
- Nutrition Department
  Pr. Jean-Michel OPPERT

Saint-Antoine Hospital Group

- Cardiology Department
  Pr. Ariel COHEN
- Endocrinology, diabetes, and reproductive medicine department
  Pr. Sophie CHRISTIN-MAITRE

Centre for Clinical Research (CCR) Paris-East

Led by Pr. Christian FUNCK BRENTANO

The Centre for Clinical Research (CCR) Paris-East is wholly dedicated to the conception, realisation, analysis and publication of physiopathology and pharmacology clinical research. The CCR prioritises areas within cardiology, endocrinology and metabolic diseases, specifically diabetes.

Centre de recherche en Nutrition Humaine [Centre for Human Nutrition Research](CHNR)

Led by Pr. Jean-Michel OPPERT

The CHNR's objective is to coordinate and harmonise research programmes in human nutrition, particularly in relation to human dietary behaviour and any determinants and consequences; to contribute to teaching, training, promotion, expertise and nutritional education; and to contribute to the transfer of technologies between the hospital sector, research laboratories and manufacturing. Its mission is to perform phenotyping/ genotyping of dietary behaviours and nutritional and nutritional status for population studies, intervention trials and physiological and pathophysiological studies.

REFERENCE CENTRES

Paris reference centre for cardiomyopathies and hereditary and rare cardiac rhythm disorders (CARDIOGEN network)

led by Pr. Philippe CHARRON

In 2014, the Minister for Heath certified the reference centre for hereditary and rare cardiac disorders as a centre of excellent for clinical care and treatment, research and training (http://www.cardiogen.aphp.fr). It is particularly concerned with cardiomyopathies on the one hand, and rhythm/conduction disorders on the other. The centre is structured as a pluridisciplinary network, with a technical platform that ensures optimal medical care and treatment. It is supported by strong research activity, in particular in connection with the JRU1166_SU/Inserm.

Integrated Specialist Centre for Obesity Ile-de-France Centre

ICAN partner: Pr. Christine POITOU-BERNERT

As an expert centre in the genetics of obesity, it aims to recognise and treat forms of obesity linked to rare diseases or genetic factors.

Reference Centre for Rare Endocrine Growth and Development Diseases

ICAN partner: Pr. Philippe TOURAINE

This reference centre brings together 5 member centres including Pitié-Salpêtrière, as well as centres of competence across France. More than 2,500 patients are currently included in the Pitié-Salpêtrière centre, who present with rare pituitary development pathologies or rare tumours of the hypothalamus-hypophysis zone such as craniopharyngioma, but also adrenal enzyme deficiencies that lead to congenital adrenal hyperplasia, sexual development abnormalities or acquired ovarian pathologies such as primary ovarian insufficiency.

Reference Centre for Rare Gynaecological Diseases

ICAN partner: Pr. Philippe TOURAINE

The centre brings together 4 member centres including Pitié-Salpêtrière, as well as centres of competence across France. More than 2,500 patients are currently included in the Pitié centre, who present with vaginal-uterine development anomalies, gynaecological complications from coagulation diseases, patients requiring a particular kind of care within a context of system diseases such as lupus or histiocytosis; and also patients from the rare growth and development endocrine diseases centre who need a specific kind of gynaecological care; and lastly, patients presenting with rare benign mammary pathologies. This centre has just obtained funding to draft a NTP (National Treatment Programme) and to create therapeutic education programmes.

Reference centre for Inflammatory diseases of the Bile Ducts and Auto-immune hepatitis.

ICAN partner: Pr. Chantal HOUSSET

The rare disease reference centre "Inflammatory Bile Duct Diseases (IBDD)-H" in the FILFOIE network and the Rare-Liver ERN coordinates 31 reference or competence centres. It has a single-centre database of 1,500 patients with primary biliary cholangitis, primary sclerosing cholangitis, genetic intrahepatic biliary lithiasis (GIBL) and autoimmune hepatitis. It participates in major international collaborative projects in this area, and had manufacturing partners.

Reference centre for Rare Insulin-Secretion and Insulin-Sensitive Pathologies (RISISP)

led by Pr. Corinne VIGOUROUX

The scope of expertise of this centre includes severe insulin resistance syndromes, including lipodystrophic syndromes and accelerated ageing syndromes, neonatal diabetes, monogenic diabetes and syndromic diabetes in children and adults. The RISISP network's mission is application, research, expertise, teaching, training and coordination of treatment, in conjunction with the rare endocrine disease network (REDN) and patient associations.

THE RESEARCH TEAMS

Research unit 1166 for cardiovascular and metabolic diseases

led by Pr. Stéphane HATEM

Created in 2014, this joint research unit is wholly devoted to research into cardiovascular and metabolic diseases around four main axes: atherothrombosis and coronary diseases, the genomics of cardiomyopathies and heart failure, atrial fibrillation and cardiac arrhythmias, lipids and atherosclerotic vascular diseases. The JRU is home to 5 teams.

- *Team 1* - Genomics and Physiopathology of Myocarditis Diseases
  led by Pr. Philippe CHARRON
  Study of the genetic variants of cardiomyopathies and canalopathies.
  Transfer to the clinic for genetic tests and high-speed sequencing.

- *Team 2* - Atherothrombosis and Applied Pharmacology
  led by Pr. Jean-Philippe COLLET
  Study of cardiovascular diseases primarily linked to atherothrombosis, from therapeutic strategies through to preventative education.
  Expertise in cardiovascular epidemiology, randomised clinical trials.

- *Team 3* - Molecular and Cell Plasticity in Cardiovascular Diseases
  led by Dr Sophie NADAUD and Dr Elise BALSE
  Molecular and cell bases of cardiovascular diseases.
  Expertise in molecular biology, cell electrophysiology and molecular imaging.

- *Team 4* - Systemic and Lipidic Metabolism in Cardiometabolic Diseases
  led by Dr Wilfried Le GOFF
  Systemic and cell metabolism of lipids and lipoproteins.
  Translational approaches and analytical tools.

- *Team 5* - Mononuclear phagocytes in cardiometabolic diseases
  led by Dr Philippe LESNIK
  The immune system, in particular the role played by mononuclear phagocytes in the development of metabolic and cardiovascular diseases.

JRU 1146 - Biomedical Imaging Laboratory (BIL) CNRS - INSERM

- *Team* - Cardiovascular Imaging
  led by Nadjia KACHENOURA, DR, INSERM
  Development of new cardiac and vascular imaging biomarkers combining cardiovascular phenotypes. Development and validation of cardiac and vascular image processing software Artfun: arterial stiffness, Mimosa: 3D aortic geometry; CardFlow: diastolic function from velocimetry images; Cardio-track: multi-cavity myocardial deformation from standard film images.

Research unit 938 - Saint-Antoine Research Centre

3 of the 13 teams from this unit are part of the HUI-ICAN

- *Team 9* - Lipodystrophies, metabolic and hormonal adaptations, and ageing
  led by Pr. Bruno FÈVE
  Study of the physiopathological mechanisms of genetic lipodystrophies, or those acquired through HIV infection or treatment with glucose-corticosteroids, as well as associated reproductive disorders. *In vivo* study (animal models, patient cohorts) and the in vitro study of the links between lipodystrophies, insulin resistance, ageing of adipose tissue, and reproductive diseases.

- *Team 11* - Metabolic and liver bile fibro-inflammatory diseases
  led by Pr. Chantal HOUSSET
  Study of genetic defects in the ABCB4 phosphatidylcholine transporter that are responsible for hereditary diseases, the cell death mechanisms that promote hepatic inflammation and fibrosis in NAFLD, and the subpopulations of hepatic myofibroblasts involved in fibrosis and the stroma of cholangiocarcinoma.

- *Team 12* - IFG system, foetal and post-natal growth
  led by Pr. Irène NETCHINE
  Study of the physiopathology of foetal growth related to imprinting pathologies in patients born small for their gestational age or presenting with excessive growth. Patient study, mouse models, and iPS approach.

JRU 1138 - Cordeliers Research Centre

- *Team* Metabolic diseases, diabetes and co-morbidities
  led by Fabienne FOUFELLE
  Understanding the mechanisms involved in the development of insulin resistance in the liver, adipose tissue and skeletal muscles, and the impairment of insulin secretion by pancreatic beta cells in type 2 diabetes. The team is studying the mechanisms that contribute to the disruption of insulin signalling (insulin resistance) and how inflammation is formed at the molecular level in the liver and adipose tissue of obese individuals, a mechanism that contributes to local and systemic insulin resistance.

JRU 1269 - Research unit: Nutrition and obesities: systemic approaches (nutriomics)
led by Pr. Karine CLÉMENT

This research unit conducts numerous foundational and translational research projects in the field of obesity and related metabolic disorders. It aims to explore the disruption of the inter-organ dialogue and particularly the role of adipose tissue and the intestines and the microbiota in these dialogues, and to identify new ways of stratifying disease and new treatments to improve cardiometabolic health.

The team's 5 principal themes are:
- Progression of obesity and related complications: role of the intestinal microbiota
- The intestines, the key to metabolic disorders
- The reshaping of adipose tissue
- The biology of systems and data integration
- Translating our foundational research into benefits for patients

MSU 37 - Mixed Service Unit
led by Stephane Le CROM

The UMS PASS platforms offer expertise in cytometry, proteomics, genomics and sample management.

THE PLATFORMS

Thanks to the future investment programme from which the HUI-ICAN has benefited, the institute has structured, in the form of scientific platforms, a unique service offer to accelerate research on cardiometabolic diseases. The 8 scientific platforms and the clinical research platform support the research mission of the scientific and medical community of the HUI. They are open to collaborations with manufacturers. Innovation is at the heart of what they do, and their complementarity is a factor in accelerating scientific projects.
The HUI-ICAN has developed exceptional operational and human capital to structure the conditions that are necessary for the emergence of a multidisciplinary management of cardiometabolic diseases. Today, the HUI-ICAN is able to offer a high level of human expertise and effective services with significant scientific added value.

Platform coordinator: Ludovic LE CHAT, Ph.D.
Clinical platform manager: Recruitment underway

8 *PLATFORMS AND* **1** *CLINICAL RESEARCH PLATFORM*
dedicated to innovation

The clinical research platform

ICAN INVESTIGATION

Located on the 1st and 6th floor of the E3M Institute of the Pitié-Salpêtrière Hospital, the clinical research platform is dedicated to biomedical research. Its goal is to contribute to the smooth running of clinical trials, and also to help sponsors and researchers participate in academic or pharmaceutical industry clinical research protocols, from the feasibility stage to project closure, thanks to its specialised teams.

TEAM
- Platform Deputy Manager: Choukri TRIQUI
- Clinical Research Doctor: Dr Raluca PAIS
- Clinical Research Nurse: Thomas MAUREL
- 9 clinical research technicians: Selma ABID, Anissa BOUABDALLAH, Stéphanie COMBET, Hanane GUERMOUDI, Hayet IDDIR, Valentine LEMOINE, Madjid OUDIHAT, Sophie SAUN, Carole BERNHARDT
- 1 radiographer: Christel DE LIRA

The scientific platforms

ICAN IMAGING

Ican Imaging is the first and only platform for human imaging dedicated to cardiovascular and metabolic clinical research in Ile de France. It includes the ICAN Imaging platform and its team of cardiovascular MRI and ICAN Imaging Core Lab, a team specialised in processing the data generated.

TEAM
- Scientific Manager: Pr. Alban REDHEUIL, Nadjia KACHENOURA, DR, INSERM
- Manager: Khaoula BOUAZIZI, Ph.D.
- Engineers: Ali KILINC, Mohamed ZARAI
- Radiographers and Imaging technicians: Mikaël PRIGENT, Philippe RATURAT, Patrick LAHADY, Romain ULLIAC

BIO-ICAN

The ICAN has a dedicated Centre of Biological Resources Le CBR Bio-ICAN, certified under number NF S 96-900 and ISO 9001, comprises collections of human matter (serum, plasma, urine, stools, tissue, ribonucleic acid (RNA), Deoxyribonucleic acid (DNA), cells etc.) in a context of foundational, translational and clinical research. The CBR ensures the processing chain: the reception, preparation, supply and preservation of samples, and accompanies researchers in the project preparation, in order to help them anticipate all the questions that might come up relating to the constitution of their collection. The CBR Bio-ICAN collaborates on numerous academic and manufacturing projects.

TEAM
Manager: Sara CIPRIANI, Ph.D.
Technicians: Jean-Baptiste BLOND, Ludivine HARMAND, Rania MAKROUF

ICANalytics

ICAN Analytics is comprised of 2 state-of-the-art platforms that respond to emerging needs in cardiometabolic research. Its objective is to identify new biomarkers in the cardiometabolic and nutrition fields, in order to improve the prevention and personalisation of treatments.

Metabolomics platform

This platform provides cutting-edge human know-how and technological expertise in metabolism research. The services offered enable high throughput quantification and profiling of all the molecules belonging to the metabolome.

TEAM
- Manager: Farid ICHOU, Ph.D.
- Scientific Manager: Philippe LESNIK, DR, INSERM
- Data Scientist: Maharajah PONNAIAH, Ph.D.
- Technician: Sora LECOCQ

Lipidomics platform

This platform offers state-of-the-art technology including mass spectrometry, coupled with gas and liquid chromatography, that enables us to guarantee quantitative and ultra-sensitive analyses of hundreds of lipid species in multiple biological matrices.

TEAM
- Manager: Marie LHOMME, Ph.D.
- Scientific Manager: Anatol KONTUSH, DR, INSERM
- Data Scientist: Maharajah PONNAIAH, Ph.D.
- Technician: Sora LECOCQ

iPSICAN

The iPSICAN platform offers a service that is still very rare in France. Its objective is to develop new cell models for cardiometabolic research. It is dedicated to reprogramming adult cells to induced pluripotent stem cells, and to their differentiation into different cell models (cardiomyocites, adipocytes, etc).

TEAM
- Manager: Vincent FONTAINE, Ph.D.
- Scientific Manager: Éric VILLARD, Ph.D.
- Assistant engineer: Sibylle MARTEAU

CYTO-ICAN

Thanks to a significant bank of equipment, CYTO ICAN can offer cell sorting, characterisation and analysis techniques. In the interests of gaining precious time in the implementation of research projects, the platform's team accompanies the researchers from the sample preparation phase. The platform can be accessed autonomously, which provides more flexibility to project leaders.

TEAM
- Manager: Florence DEKNUYDT, Ph.D.
- Research Engineer: Aurélie GESTIN

ICAN HUMAN HepCell

ICAN HUMAN HepCell produces preparations of human liver cells and tissues and develops in vitro models of hepatic pathologies. It specialises in preclinical research for the development of human cell and tissue models in primary cultures, in order to study the molecular mechanisms of chronic liver diseases (steatosis, NASH, fibrosis, cirrhosis, etc.) and to test the efficacy of the therapeutic molecules proposed by pharmaceutical industries, before clinical evaluation.

TEAM
- Manager: Lynda AOUDJEHANE, Ph.D.
- Scientific Managers: Pr Filomena CONTI, Pr Chantal HOUSSET
- Technician: Lisa Alcaide DESCHAMPS

PreclinICAN

ICAN's pre-clinical platform, located on the Pitié-Salpêtrière Hospital site, enables metabolic phenotyping in the field of cardiometabolic and nutritional diseases (obesity, diabetes, dyslipidemia, NASH, heart disease, etc.) in the context of academic projects. In particular, it enables *in vivo* insulin resistance measurement, and body composition analyses.

TEAM
- Manager: Amélie LACOMBE
- Scientific Manager: Thierry HUBY, PhD

AXIS 1

NEW INTERFACES BETWEEN METABOLIC AND CARDIOVASCULAR DISEASES

INTESTINAL MIOCROBIOTA AND CARDIOVASCULAR DISEASES

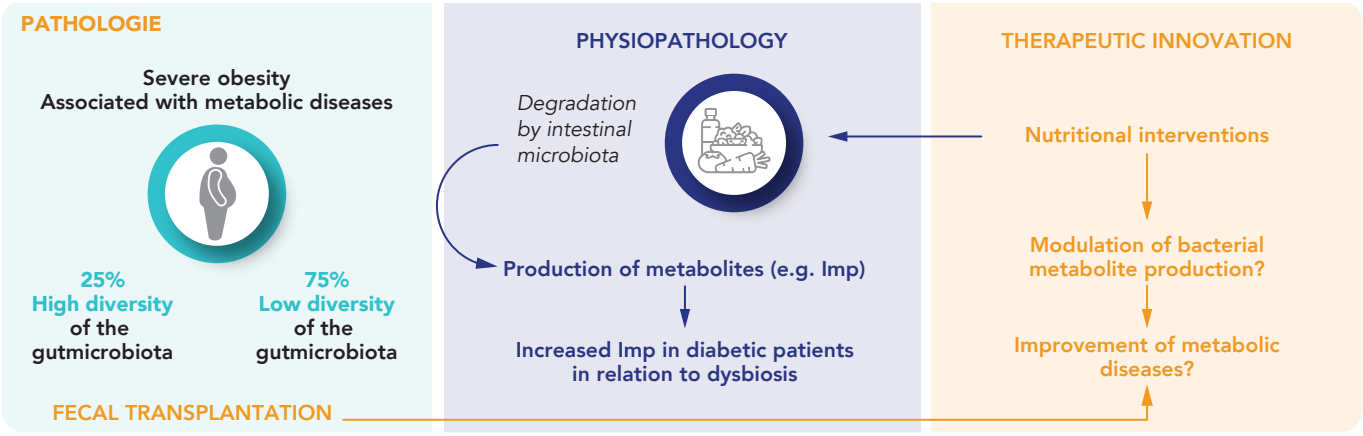
Dr J. ARON-WISNEWSKY
University lecturer - Hospital Practitioner, Nutrition Department - cardiometabolism pole

The microbiota, a promising option

The nutriomics team, managed by Pr. Karine Clément, contributed to the identification of the relationship between cardiometabolic diseases (CMD) and the intestinal microbiota, particularly understanding why intestinal dysbiosis promotes metabolic diseases (Aron-Wisnewsky et al., Nature reviews hepato-gastro 2019; Aron-Wisnewsky et al., Gastrolenterology 2020, Aron-Wisnewsky et al., Gastrolenterology 2021) Microbial genetic diversity (MGD) drops during obesity and metabolic diseases (Aron-Wisnewsky Gut 2018), with an increased prevalence in the most severe forms of obesity. While murine studies have shown an increase in intestinal permeability during obesity or following a fat-rich diet, in humans the intestinal barrier is only subtly compromised in a fasting obese person. However, this changes for those on a fatty diet (Genser J Pathol 2018). Inversely, raised microbial diversity is associated with healthy eating habits (Dao Front Physiol, 2019). Bariatric surgery, which leads to weight loss and improves metabolic diseases, changes the composition of the microbiota and increases microbial genetic diversity. Yet, this does not always enable a return to the levels of patients with a standard body type (Aron-Wisnewsky Gut 2018). The MétaCardis cohort, put together within the context of an FP7 European project and co-financed by the HUI-ICAN, has shown that statin treatment improves the drop in genetic microbial diversity in patients with cardiometabolic diseases (Vieira-Silva S. et al., Nature 2020). However, the intestinal microbiota produces metabolites from the breakdown of ingested food. Some of these metabolites are involved in metabolic diseases. Thus, imidazole propionate derived from the bacterial metabolism of certain nutrients is increased in type 2 diabetic patients and associated with the presence of microbial dysbiosis (Molinaro et al., Nature communication 2020).

Progress for patients

This research work has led to the creation of nutritional intervention studies aimed at evaluating the impact of diet on the dysbiosis of the microbiota and the production of metabolites such as Imidazole propionate, on the one hand, and on the glycaemic balance of patients with type 2 diabetes, on the other (European JPI project). Innovative therapeutic projects will start soonsuch as, in particular faecal transplantation, in the form of oral capsules, which could improve the glycemic balance in diabetic patients (PHRC National Drifter Principal Investigator Dr. Aron-Wisnewsky).



ADIPOSE TISSUE: NEW INTERFACE BETWEEN CARDIOMETABOLISM AND CARDIOVASCULAR DISEASES

Pr Stéphane HATEM
Director of Unit 1166 for cardiovascular and metabolic diseases, Chief Executive of the HUI-ICAN

Dr Elise BALSE
Lecturer, Sorbonne Université [Sorbonne University]
JRU 1166 - molecular and cell plasticity in cardiovascular diseases

The HUI-ICAN, a pioneer in describing the role of fatty tissue in cardiometabolic diseases.

Fatty tissue is one of the primary interfaces between metabolism and organs in general, in particular, and the heart and vessels.

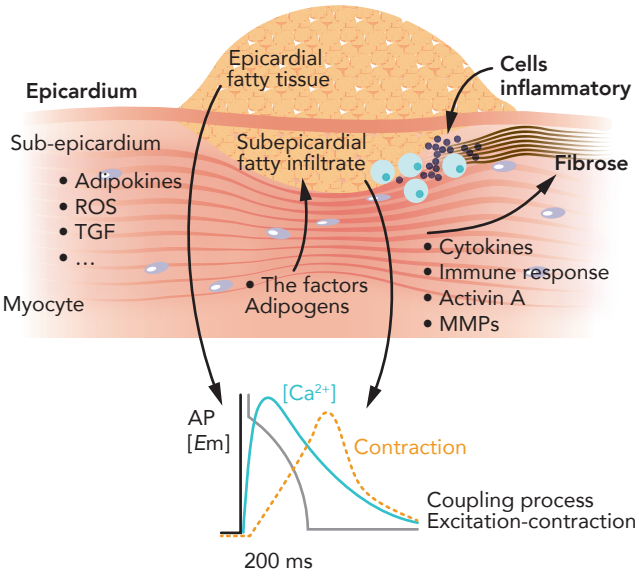
The HUI-ICAN teams have pioneered the description of how the fatty tissue around the heart plays a role in the risk of onset of the most common cardiac arrhythmias, auricular fibrillation. They showed that this fatty tissue can, under some circumstances, promote atrial myocardium fibrosis, a mechanism of arrhythmias (Ventecleft et al., Eur Heart J 2016).

These teams identified the origin of this cardiac fatty tissue, which comes from the differentiation of progenitor cells residing in the external layer of the heart, the epicardium. The recruitment of progenitor cells and their differentiation into fat cells occurs during various cardiac stresses: too much work or metabolic stress (Suffee et al. Circ Res 2020). These discoveries have opened new research perspectives on cardiac arrhythmias, in particular on the impact of metabolic diseases, obesity, metabolic syndrome, diabetes, and on the accumulation of cardiac fatty tissue and its biological activity (Chua W et al. BMC Cardiovasc Disord. 2019).

New research perspectives

Another axis of research aims to determine whether cardiac fatty tissue can be a biomarker of the progression of myocardial remodeling and the formation of the substrate for atrial fibrillation. To answer this question, the HUI teams have shown that the close study of the deformation of the wall of the atria analysed by MRI imaging - thanks to software developed by researchers at the LIB (Biomedical Imaging Laboratory) - provides information on the degree of infiltration of the myocardium by fatty tissue and fibrosis and thus on the progression of the substratum of atrial fibrillation (Hubert Radiology 2018). This work, on the development of the biology of the atrial myocardium and the progression of the substratum of atrial fibrillation is being continued in the context of a large European H2020 MAESTRIA consortium (led by Pr. Stéphane Hatem).

IMPACT OF CARDIAC FATTY TISSUE ACCUMULATION ON THE RISK OF CARDIAC ARRHYTHMIA



WHAT IS THE ROLE OF CHOLESTEROL IN CORONARY EVENTS?

Maryse GUERIN
Director
of research
JRU_S 1166

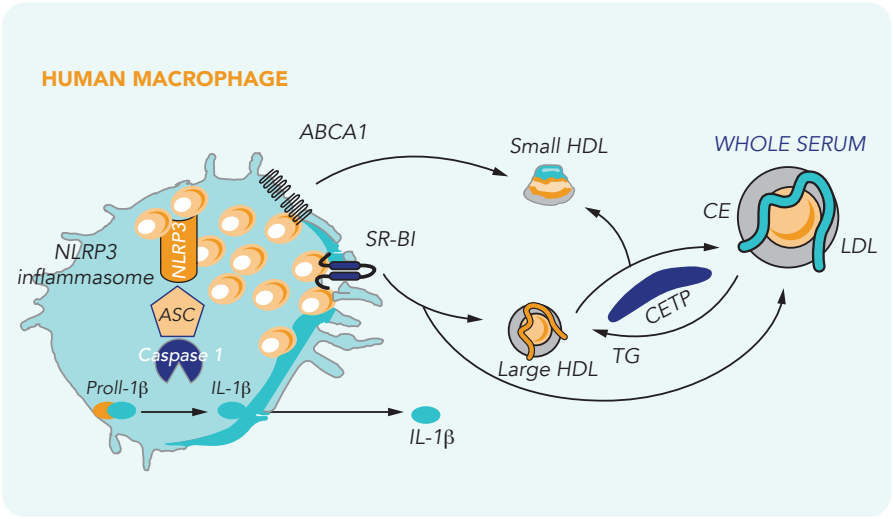
Pr. Johanne SILVAIN
Cardiologist

Pr. Éric BRUCKERT
Endocrinology, Metabolism and Prevention of Cardiovascular Diseases Manager of a specialist centre for congenital hypercholesterolemia

Despite significant therapeutic progress, cholesterol remains a significant risk factor in the onset of atherosclerosis of the arteries, and in particular in coronary events. Pr, Eric Bruckert leads a team that is *the* reference in the care and treatment of cholesterol-related cardiovascular diseases, in particular congenital hypercholesterolemia, one of the most frequent genetic diseases responsible for cardiovascular diseases affecting young patients. This equipment has contributed a great deal to the evolution of medical practices by establishing the recommendations published by European learned societies (eur Heart J 2020)

For some years, the HUI-ICAN researchers (teams 4 and 5 JRU 1166) have been studying the transport of cholesterol from its digestive absorption, its metabolism in the liver, all the way to exchanges with the body's cells. Their work has contributed to establishing the athero-protective role of HDL particles, or "good" cholesterol. An important discovery is that the athero-protective role of HDLs is not linked exclusively to their circulating concentration (HDL-C), but also to their biological function. HDLs control the reverse cholesterol transport pathway (RCT), i.e. the centripetal movement of free cholesterol from peripheral tissues such as the vascular wall, to the liver. The first stage of RCT is the exit, the "efflux", of cholesterol to extracellular cholesterol acceptors such as HDLs and apoAI. Changes in cholesterol efflux mechanisms lead to cholesterol accumulation in the myeloi cells, which activates the NLRP3 inflammasome and induces IL-1β production, which increases the accumulation and retention of neutrophils in atherosclerotic plaques. Thanks to a collaboration between foundational and clinical researchers at the Institute of Cardiology, Johanne Silvain and Gilles Montalescot, and with the help of the Action group (www.action-coeur.org), it was shown that serum cholesterol efflux capacity is independently associated with short- and long-term survival in post-myocardial infarction patients.

Thus, serum cholesterol efflux capacity could be a biomarker that enables identification of patients at high risk of early mortality following acute coronary occlusion. Recent work by these researchers shows that elevated concentrations of IL-1β upon admission are associated with an increased risk of cardiovascular mortality at 3 months in post-myocardial infarction patients. An elevated concentration of IL-1β identifies the patients at risk of early post-infarction mortality who should receive more tailored treatment, combining lipid-lowering agents and inflammation inhibitors.



THE LIVER, A HUB OF CARDIOVASCULAR AND METABOLIC DISEASES: THE ROLE OF NASH *(Non-Alcoholic SteatoHepatitis)*

Dr Raluca PAIS
Gastroenterologist and hepatologist

Pr Vlad RATZIU
Gastroenterologist and hepatologist

Non Alcoholic Fatty Liver Disease (NAFLD) affects about 25% of the general population and is the leading cause of chronic liver disease. This presents significant public healthcare challenges, with very high annual treatment and care costs. NAFLD is a multi-system disease at the centre of cardiometabolic pathologies closely related to insulin resistance and adipose tissue dysfunction. The NAFLD spectrum covers two entities with different evolutions and prognoses: isolated steatosis and steatohepatitis (NASH - non alcoholic steatohepatitis).

NASH is associated with the progression to cirrhosis and its hepatic complications (hepato-cellular carcinoma), as well as cardiovascular diseases and type 2 diabetes.
Within ICAN, at the impetus of Pr. Vlad Ratziu, research teams and clinical departments have developed a multi-disciplinary translational research activity "*from bench to bed side*", involving cardiologists, radiologists and nutritionists, based on unique national and international patient cohorts.

Productive and collaborative translational research

•The HUI is a partner in the European Horizon 2020 Consortium 2020, EPoS - Elucidating Pathways of Steatohepatitis) and coordinates the multi-center international project HOTSURFER, which aims to better understand the natural history, progression factors and comorbidities of NASH. Consequently, the team identified the relationship between NAFLD and early coronary atherosclerotic lesions, the relationship between NASH and sarcopenia, and the benefit of bariatric surgery for patients with NASH and advanced fibrosis.

• The HUI-ICAN teams have validated new histological classifications for NASH and shown that histological liver involvement correlates with the clinical phenotype.

•The HUI-ICAN is a participant in the European LITMUS project (European IMI2 Funding) whose goal is to develop biomarkers to diagnose and monitor patients with NAFLD.

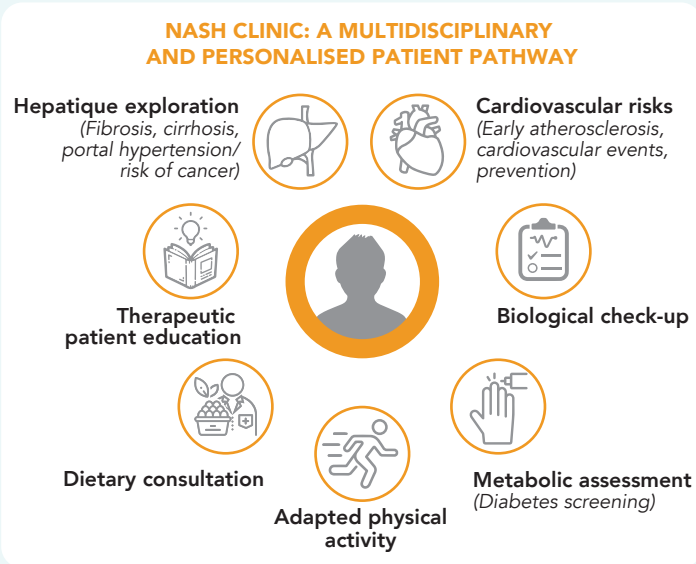
• The HUI is the lead participant for NASH, in the formulation of a new model of treatment trials within the framework of the European EU-PEARL (European Patient Centric Clinical Trial Platform) (IMI2 and EFPIA Funding) with the goal of improving the design of clinical trials and accelerating the development of different molecules, with patient involvement in these treatment trials.

The NASH clinic: *first hospital structure with multidisciplinary care for patients with metabolic steatosis.*

All this research activity is for the benefit of the patients, via the creation of a **unique reference center in France** for the multidisciplinary treatment and care of patients with metabolic steatosis: the NASH clinic.

It is the **first hospital structure for multidisciplinary care** organised in a unified and fluid patient circuit in an out-patient setting, with additional state-of-the-art investigations:

- **Hepatic** (severity of liver damage determined by non-invasive methods).
- **Cardiovascular** (Coronary Calcium Score to identify early atherosclerotic lesions) and cardiovascular risk assessment.
- **Metabolic** (determination of body composition by DXA, assessment of insulin resistance and metabolic comorbidities).
- Every patient also has a **treatment education** consultation, a dietary evaluation, a summary medical consultation and a 6-month follow-up with an assessment of the improvements in metabolic status and the implementation of dietary and physical activity steps.



AXIS 2
CARDIOMETABOLIC DISEASES: THE LIFETIME DISEASES

The pathophysiological process that leads to the onset of cardiovascular and metabolic diseases begins very early in life. In addition to the genotype, which determines the risk factors of every individual, the parents-foetus relationship, less understood, may also play a determining role, for example in the onset of diabetes. The other characteristic is the existence of a long clinically-silent phase where lifestyle, nutrition and comorbidities play their part. Then, most often, it is an acute episode that reveals the progress of the physiopathological process and tips a healthy individual into the 'patients suffering from chronic diseases' group.
The challenge is to be able to identify and intervene early on in the phases of this physiopathological continuum, to avoid the silent development of chronic diseases, to better manage acute episodes, and to do everything possible to ensure that patients preserve a good quality of life.

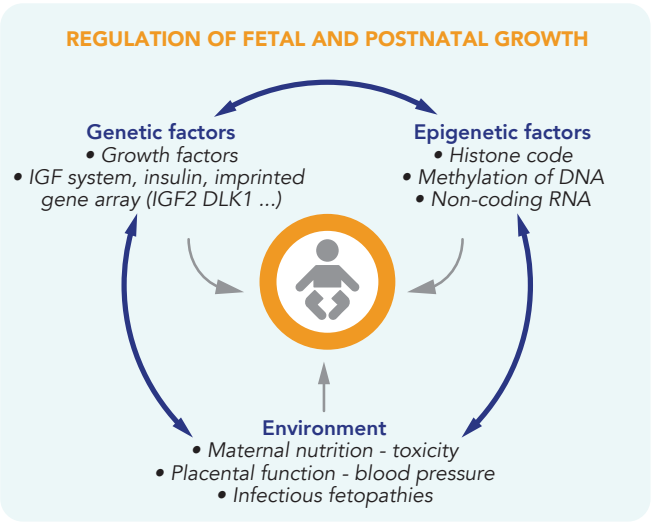
PARENTS/CHILD IMPRINTING AS A PREDISPOSING FACTOR IN LIFETIME TRAJECTORIES

Pr. Irène NETCHINE
Paediatrician
Director of the INSERM U938 research unit, CRSA, IGF System, fœtal and postnatal growth

Imprinting disorders represent a group of rare diseases, which frequently affect foetal and/or postnatal growth, placental function, metabolic homeostasis and behavior. Thus, underweight fetuses have a higher risk of developing visceral fat deposits and insulin resistance in the postnatal period (concept of a developmental origin of health and diseases). At the other end of the spectrum, macrosomia is associated with neonatal hyperinsulinism, increased adiposity and organomegaly.

Intrauterine growth as a determining factor in a child's trajectory

With the support of the HUI-ICAN, we have shown in a preclinical model that intrauterine growth restriction determines weight gain, insulin resistance, and arterial hypertension in adulthood and that early life nutrition is a major factor in this mother-foetal programming (Saget et al., Mol Met 20). In growth restriction, molecular signatures can be detected in organs before the onset of any clinical signs of metabolic disease. In particular, there is an abnormal accumulation in the blood of certain non-coding RNAs, the microRNAs, which could constitute predictive circulating biomarkers of metabolic diseases. This would then, allow for upstream, precision medicine. Another biomarker concerns the diagnosis of intrauterine growth restriction. The detection of foetuses who will be born small for their gestational age (SGA) early in the pregnancy, improves foetal and neonatal prognosis, but to date there is no good biomarker of foetal restriction during pregnancy. The preadipocyte factor PREF1, also called Delta-like homolog 1 (DLK1), is a non-canonical transmembrane ligand of the Notch voice. We have just shown that maternal blood levels



of DLK1 are significantly decreased in pregnant women at 36 weeks' gestation who go on to deliver babies with a low birth weights (Pham et al, submitted).

Better understanding for better care

The HUI-ICAN teams have put together cohorts of patients with rare and extreme forms of adipose tissue diseases most often linked to a unique molecular mechanism that may allow a better understanding of the pathophysiology of the frequent and multifactorial forms of metabolic diseases. Thus, abnormalities affecting the interactions between chromatin and certain transcription factors could be in the lipodystrophies associated with lamin A/C mutations, or the rare growth retardation of Silver-Russell syndrome.

The iPSCs technology used on ICAN's iPS platform, allows the reprogramming of somatic cells taken from a patient into a stem cell capable of differentiating into mature mesenchymal cells, and provides an original approach to studying the consequences of imprinting diseases in different tissues. Thus, the team is developing an iPSc model generated by patients with Silver-Russell syndrome as well as those who present with the mirror opposite syndrome, who have excessive growth, Beckwith Wiedemann syndrome (BWS). The idea is then to differentiate these iPSCs into chondrocytes and adipocytes.

SUPPORTING THE JOURNEY FROM CHILDHOOD INTO ADULT LIFE

Pr. P. TOURAINE
Head of the Endocrinology and reproductive medicine department

There are more than 500 metabolic and endocrine diseases. Many of these diseases are rare (incidence rates ranging from 15 per 100,000 to less than 1 per 1,000,000) with very diverse clinical pictures, but they all start in childhood and require lifelong medical care and treatment.

Initiated in 2017 by Pr. Touraine, head of the endocrinology and reproductive medicine department, the TRANSEND project is based on a simple observation, that too many patients are "lost from sight" during their 'transition', i.e. when they move to the adult sector, after a childhood in the very protective environment of a paediatric hospital.
The many reasons (desire to have a normal life, becoming bored of their treatment) that explain these breaks in treatment and care now find an answer with the TRANSEND programme and its dedicated non-medical space, located on the first floor of IE3M.

This programme's ambition is to accompany and give autonomy to young people between 15 and 25 years old, who are sufferers of chronic diseases and who start their follow-up as adults in the endocrinology, diabetology and nutrition departments of IE3M.

Led by a care pathway coordinator, TRANSEND has helped more than 630 patients in 4 years, with 95% of them being seen in individual consultations. A second appointment was held in 30% of cases, upon request of a doctor; these were held during times when the patients were hospitalised, or in out-patient care.

Lastly, through TRANSEND more than 300 patients have had an appointment with a dietician, a psychologist or a social worker. Recently this programme has really proven its efficiency, with more than 88% of patients in transition seen regularly in the adult sector (Le Roux et al., 2020).

TRANSEND

MANAGEMENT OF ACUTE EPISODES TO IMPROVE CHRONIC PHASES

Cardiometabolic diseases (CMD) are often revealed by acute episodes of organ dysfunction. In addition to acting as vital prognostic indicators, these acute episodes determine the timeline of CMDs' progression and a patient's quality of life during the chronic phases.

Pr. Alain COMBES
Intensive care medicine department

Pr. Pascal LEPRINCE
Thoracic and cardiovascular surgery department

INNOVATION HELPING PATIENTS WITH SEVERE HEART FAILURE

The HUI-ICAN teams have profoundly changed the prognosis for acute episodes, by developing a unique expertise in circulatory and ventilatory support. With his medical intensive care team, Pr. Alain Combes is one of the international leaders in the treatment of cardiac-respiratory failure using extracorporeal membrane oxygenation (ECMO) techniques. This team conducted a landmark international, multi-centre clinical trial, EOLIA (Combes NEJM 2018; Goligher JAMA 2018), which defined the use of these circulatory support and extracorporeal oxygenation techniques in the treatment and care of patients with severe heart failure complicating the acute phase of myocardial infarction.

The team is also developing translational research projects on the mechanisms of generalised oedemas in patients admitted to intensive care for severe heart failure. They have shown that a leak from the endothelial barrier of the vessels occurs, which leads to the passage of plasma from the vascular compartment towards the tissues. Several proteins have been identified as the cause of this vascular leak, one of which is currently the target of a treatment trial in humans.

STATE-OF-THE-ART COLLABORATIVE RESEARCH TO IMPROVE THE TREATMENT AND CARE OF PATIENTS WITH SEVERE HEART FAILURE

The cardiac surgery department headed by Pressor Pascal Leprince is the leading department in France in terms of clinical activity and, in particular, in treatment and care of terminal heart failure by heart transplantation, thanks to the development of circulatory support techniques.

In 2019, Pr. Pascal Leprince's team set up the CALYPSO public-private partnership project between the HUI-ICAN, the Lille CHRU [Regional University Hospital, RUH] and the company CorWave, with the help of the Banque Publique d'investissement [Public Investment Bank (BPI)]. This project aims to improve permanent cardio-circulatory support systems for patients with severe heart failure. This novel idea is that this pump system mimics the pulsatile nature of blood flow in the body to minimise the activation of coagulation and the formation of clots. This is a bench-to-patient project requiring the development of an ovine pulsatile left mono-ventricular assist model.

CIRCULATING LIPIDS OF HEPATIC ORIGIN AS A PREDICTOR OF TYPE 2 DIABETES

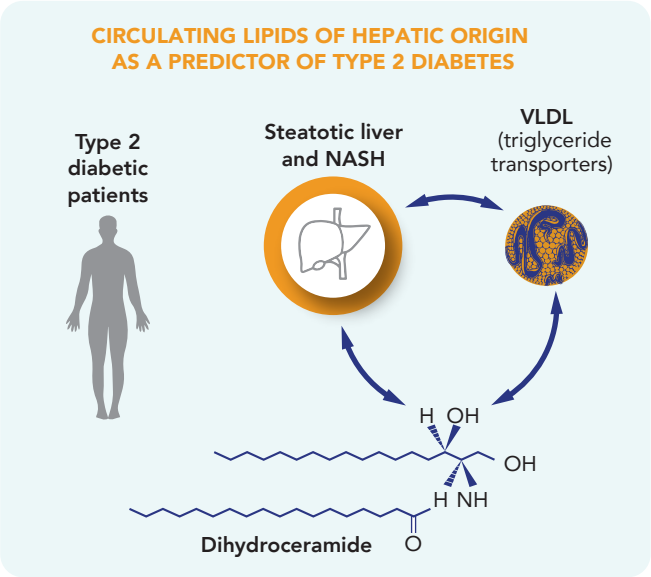
Fabienne FOUFELLE
Team Leader, Inserm 1138
Metabolic diseases, diabetes
and co-morbidities
Cordeliers Research Centre

Dr Olivier BOURRON
Department
of Endocrinology and Metabolism

Dihydroceramides (DhCer) are lipid compounds in the sphingolipid family. These are major constituents of all cells, present particularly in the membranes, and they are involved in many aspects of cell biology such as proliferation and survival.

Previous studies by the HUI-ICAN's clinical and foundational diabetology teams have shown that dihydroceramides are among the best predictors for the onset of type 2 maturity diabetes (T2D), characterised by an increase in plasma concentrations of these lipid compounds, a true biomarker of the disease.

The team has more recently tried to understand why dihydroceramides are associated with a risk of diabetes. Their work has demonstrated a correlation between blood levels of dihydroceramides and biomarkers of another metabolic disease, NAFLD: Steatotest and Fatty Liver index (FLI) for hepatic steatosis, NASHtest for NASH. The more the markers of steatosis or NASH increase, the higher the circulating dihydroceramide concentrations become. Some blood carriers of triglycerides synthesised by the liver, VLDLs, are involved. In the case of hepatic steatosis or NASH, patients secrete dihydroceramide-enriched VLDLs. These results provide an understanding of the predictive effects of DhCer on the onset of T2D, since patients with steatosis have an increased risk of T2D, and the overproduction of VLDL is one of the characteristics of diabetic dyslipidaemia. The role of DhCer enrichment in the synthesis or secretion of VLDLs is not yet understood.



Carlier Aurélie, Phan Franck, Szpigel Anais, Hajduch Eric, Salem Joe-Elie, Gautheron Jérémie, Le Goff Wilfried, Guérin Maryse, Lachkar Floriane, Ratziu Vlad, Hartemann Agnès. Ferré Pascal, Foufelle Fabienne, Bourron Olivier**

**equal contributions*

Dihydroceramides in Triglyceride-Enriched VLDL Are Associated with Nonalcoholic Fatty Liver Disease Severity in Type 2 Diabetes. Cell Rep Med. 2020 Dec 22;1(9):100154.

REPAIR OF ENDOCRINE PANCREAS DYSFUNCTION IN DIABETES THROUGH BARIATRIC SURGERY

Pr Fabrizio ANDREELLI
Endocrinology and metabolism department INSERM JRUS1269, Sorbonne Université [Sorbonne University]

Back in the 1990s, it was proven that bariatric surgery (Roux-en-Y or RYGBP, a technique that excludes most of the stomach, duodenum and proximal jejunum from the food circuit) could, within a few days, before any significant weight loss, improve or even eliminate Type 2 Diabetes (T2D) with specific effects on insulin secretion.

To better understand this observation, bariatric surgery developed by Pr. Fabrizio ANDREELLI was performed on Ob/Ob mice (mouse model for T2D). Interestingly, in this model, diabetes disappeared postoperatively despite persistent obesity, thanks to a significant improvement *in vivo* insulin secretion, more insulin in the pancreatic islets, and an improvement in the functionality of the pancreatic islets *in vitro*. This restoration of insulin secretion was dependent on changes in the expression of 27 non-coding microRNAs (miRNAs) involved in the regulation of the 193 genes that are important for pancreatic beta cell functionality. It was then shown that the recovery of T2D in humans after surgery was correlated with the expression of the 4 miRNAs identified in Ob/Ob mice as central to the regulation of the genes involved in the repair of the pancreatic islets.

The results of this study conclude that bariatric surgery can reestablish insulin secretion irrespective of any weight loss, by restoring the key functions involved in the secretion of insulin. This is, thanks to 4 core miRNAs that are identical in humans and mice. This signature probably reflects similar endocrine pancreas repair mechanisms in the two species.

GASTRIC BYPASS TECHNIQUE IN HUMANS AND MICE

Fig. 1A
Gastric bypass technique in humans

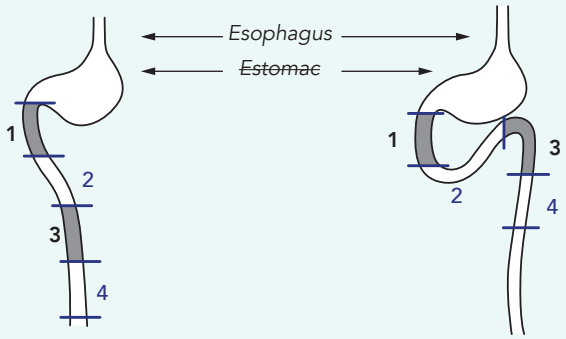


Fig. 1B
Murine equivalent developed by Pr.Fabrizio Andreelli

References:
A surrogate of Roux-en-Y gastric bypass (the enterogastro anastomosis surgery) regulates multiple beta-cell pathways during resolution of diabetes in ob/ob mice. Chloé Amouyal, Julien Castel, Claudiane Guay, Amélie Lacombe, Jessica Denom, Stéphanie Migrenne-Li, Christine Rouault, Florian Marquet, Eleni Georgiadou, Theodoros Stylianides, Serge Luquet, Hervé Le Stunff, Raphael Scharfmann, Karine Clément, Guy A. Rutter, Olivier Taboureau, Christophe Magnan, Romano Regazzi, Fabrizio Andreelli. EbioMedicine 2020 Jul 30;58:102895. DOI: 10.1016/j.ebiom.2020.102895

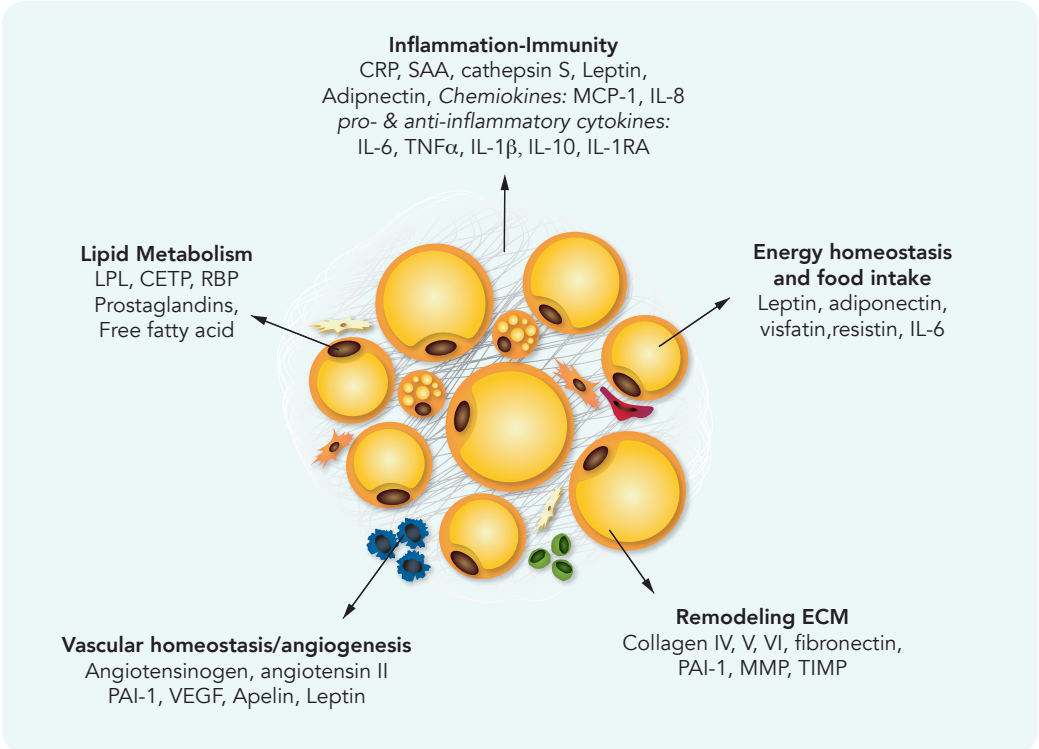
SIGNIFICANT ADVANCES IN UNDERSTANDING THE MECHANISMS OF LIPODYSTROPHIES

Bruno FÈVE
Team Leader Inserm JRU-S938
Lipodystrophies, metabolic and hormonal adaptations, and ageing

The "Lipodystrophies, metabolic and hormonal adaptations, and ageing" team studies genetic and acquired forms of lipodystrophies, including their consequences on systemic metabolic adaptations and ageing, and their impact on fertility and reproductive functions. We are resolutely developing a cross-sectional approach including molecular and cellular pathophysiology, genetic diagnosis, and the clinical and biological determinants that influence metabolic, endocrine and cardiovascular prognosis, and the study of new therapeutic strategies aimed at preventing or treating lipodystrophies.

Over the course of the past 3 years we have, in particular:

- **identified new molecular entities** responsible for genetic forms of lipodystrophies or lipomatosis, in close collaboration with the Centre de Référence des Maladies Rares PRISIS [PRISIS Reference Centre for Rare Diseases];
- **shown the deleterious metabolic** role on adipose tissue of integrase inhibitors, which are widely used in the treatment of HIV infections;
- **documented the role of glucocorticoid** signalling in the adaptation of adipose tissue and the endocrine pancreas to insulin resistance;
- **characterised** the first spontaneous rodent model of polycystic ovary syndrome and its close link to the metabolic phenotype.



THE HUI-ICAN, AS CONNECTED AS POSSIBLE CLOSER TO THE DAILY LIFE OF PATIENTS TO HELP THOSE SUFFERING FROM DIABETIC FOOT

Chronic foot wounds and amputation are serious complications of diabetes, and acute episodes in patients' lives. In 2012, diabetic foot affected approximately 350,000 people in France, 15% of diabetics, and resulted in 28,000 hospitalisations, which represents 3 billion euros' annual spending on diabetes.

The HUI-ICAN is working on several projects around diabetic foot, to improve the care and treatment of patients.

Dr Georges HA VAN
Specialist, Physical Medicine and Rehabilitation
Head of the Diabetes Podiatry Unit
Chair of the "Diabetic Foot" working group
of the Société Francophone du Diabète
[Francophone Diabetes Society]

Smart offloading footwear project

Offloading diabetic foot wounds is the most urgent treatment because it's what prevents them getting worse. 90% of diabetic foot wounds are painless, a consequence of diabetic neuropathy. Poor observance of offloading is mostly a result of this absence of pain, despite the wound. In comparison the very visible disadvantages of offloading footwear are: poor aesthetic tolerance, discomfort, limited secondary walking, having to wear a different shoe on the offloading side, etc.
A new pair of offloading shoes has been developed by Dr George Ha Van to compensate for these disadvantages. In collaboration with Engineering students from Sorbonne University, he is working on improving this new pair of off-loading shoes by installing pressure sensors that make the shoe "smart" by constantly checking its compliance, which ensures that plantar wounds can heal.

Thinking about a medical device for the prevention of foot ulcers among at-risk patients

The problem of recurrent diabetic foot wounds is a common issue globally. There is a 40% recurrence in the first year after healing, according to 19 international studies. This healing is therefore only remission, and not recovery, for patients.
An effective wound recurrence prevention tool would be a significant advantage in improving patients' quality of life.
To this end, a connected insole capable of alerting the patient of a future onset of a wound is in development by Dr Ha Van, in collaboration with a manufacturing partner.

COVIPIED STUDY

In 2020, the network of clinicians created by Dr Georges Ha Van also received ICAN's support for the implementation of a project on the impact of the 1st coronavirus/ COVID 19 pandemic quarantine on the healing time of foot wounds.
Dr Georges Ha Van is coordinating a national, retrospective, multi-centric study on diabetic foot wounds. The aim is to measure the effect of quarantine on the healing time of foot wounds of patients cared for by hospital-based services main objective of the study is to compare the outcome of diabetic foot wounds at 6 months that led to a consultation between the 1st of February and the 16th of March in 2019 (the "control" year) and 2020 (the year in which there was a strict quarantine, from 16th March to 11th May 2020).
This retrospective study involves more than 1,000 patients in 7 French multidisciplinary diabetic foot care centers.

Charcot's foot, or diabetic neuroarthropathy, is a rare and specific form of neuropathic diabetic foot

The group of clinicians chaired by Dr Ha Van has helped to map out and assess the national management of Charcot's foot in order to identify it earlier on and be able to treat it more innovatively.

ICAN's support opens up numerous possibilities to facilitate partnership, providing added value to the research being conducted for structuring and creating added value through the partnerships it facilitates.

AXIS 3
NEW MULTI-ORGAN APPROACHES FOR NEW BIOMARKERS

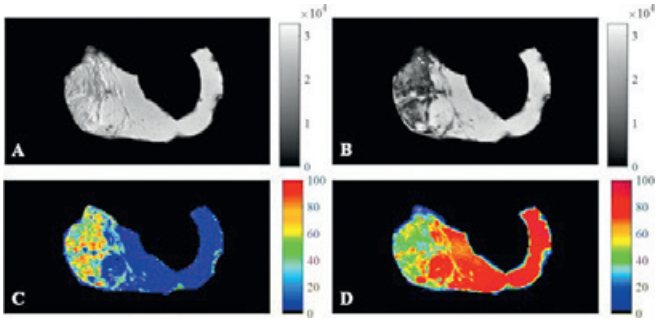
MAGNETIC RESONANCE IMAGING, AN ESSENTIAL TOOL FOR THIS MULTI-ORGAN APPROACH

Pr. Alban REDHEUIL
Head of Cardiovascular and Thoracic ICT Imaging at Pitié-Salpêtrière, Clinical Scientific Manager of the HUI-ICAN imaging platform

Nadjia KACHENOURA
Manager, Cardiovascular Imaging Team - Biomedical Imaging Laboratory; Manager, scientific methodology of the imaging platform - HUI ICAN

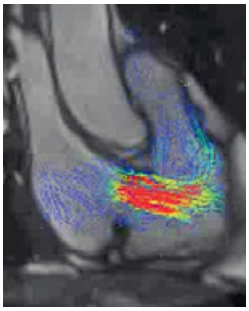
After several decades of continuous improvement in imaging aimed at better visualising the anatomy and quantifying the function of various organs, imaging for *in vivo* tissue characterisation of perfusion, fibrosis, fat, inflammation and metabolism is now emerging. The new concept of imaging "biomarkers" is now firmly established and the advanced phenotyping made possible by techniques such as MRI, CT, scintigraphy, ultrasound or optical imaging enables us to open up unprecedented windows of exploration in humans in the field of cardiometabolic diseases. The HUI ICAN, which relies on the cardiovascular radiology expertise of Pr. Alban Redheuil and the INSERM research team led by Nadjia Kachenoura, has chosen to invest significantly in this area with the acquisition of an MRI dedicated to research in cardiovascular imaging in humans. This tool, adapted to population-based imaging studies, coupled with AI technologies and omics data, enables the development of new diagnostic strategies, prognostic evaluation and personalised patient care and treatment.

Non-invasive tissue imaging to replace biopsies?



New MRI tissue mapping techniques enable *non-invasive* and risk-free (for the patient) detection and quantification of the presence of interstitial or scar fibrosis within the myocardium as well as oedemas present in inflammatory or ischemic processes. Myocardial perfusion at rest or under pharmacological stress, as well as the quantity and quality of myocardial and epicardial fat, can also be analysed. These imaging biomarkers are particularly useful for characterising the effects of arterial hypertension, diabetes and obesity on the myocardium. Thus, the ICARD study will shed light on the effect of dapagliflozin on myocardial function and composition in cardiac insufficiency among diabetic and non-diabetic subjects. These new tissue biomarkers also allow for earlier diagnoses and more relevant evaluation of the severity of numerous cardiomyopathies. The METACARDIS cohort, conduct thanks to Europe and the HUI ICAN, has made it possible to set up an ancillary study: METACARDIS-MRI, to identify MRI myocardial signatures corresponding to different stages of cardiometabolic diseases.

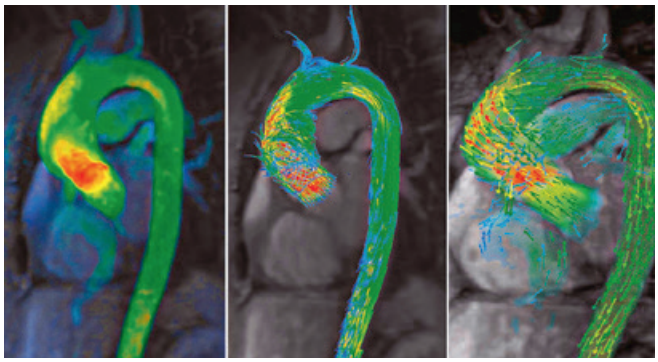
Functional imaging of the myocardium: fluid-structure interaction



The left atrium and the left ventricle and aorta form a chain of structurally and functionally interdependent links. The ICAN Imaging team has developed image processing tools to quantify this connection in cardiovascular MRI. Thus it has been possible to show the link between contractile function measured *in vivo* by MRI and fibro-fatty infiltration quantified by histology with surgical samples of the atrium (Huber A., Radiology). This type of approach, comparing multimodal imaging with histology and biology of the myocardium will be continued within the context of a European H2020 project, MAESTRIA.

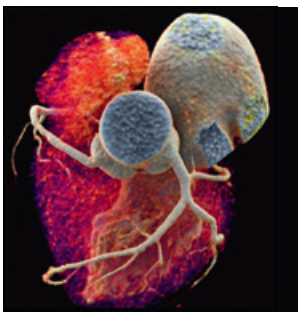
Cardiovascular age and aortic risk?

The ICAN imaging team has developed new biomarkers of arterial age, a significant prognostic factor for mortality and the onset of cardiovascular diseases and events. As a matter of fact, aortic stiffness measured by MRI is correlated with mortality and severe cardiovascular events in the general population (Redheuil A. et al. Hypertension, JACC). Similarly, 3D measurements of the aorta have been shown to be superior to 2D measurements in detecting early changes in aortic geometry (Dietenbeck et al. JMRI). However, these markers of stiffness or geometry, as well as new indices derived from intra-aortic blood flow such as pressure, shearing forces, and spatial-temporal distribution of vortices now need to be validated in the context of aortic aneurysms. This is the aim of a forthcoming European EIT Health project, conducted by 5 European partners to establish the ability of multi-parametric MRI biomarkers to improve therapeutic decision-making, care and treatment of aortic aneurysms.

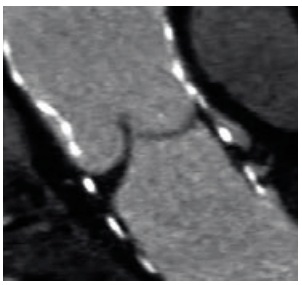


Structural and interventional cardiology and imaging

The ICAN Core Lab has carried out a CT analysis of the largest cohort of post-TAVI (Transcatheter Aortic Valve Implantation) subjects, as part of the international ATLANTIS study led by the Action Group (Pr. Jean-Philippe Collet, Pr. Gilles Montalescot).



The ongoing FH-CALC study aims to quantify coronary plaque components in subjects presenting with congenital hypercholesterolaemia.



IDENTIFYING NEW BIOMARKERS FOR METABOLIC DISEASES USING OMICS METHODS

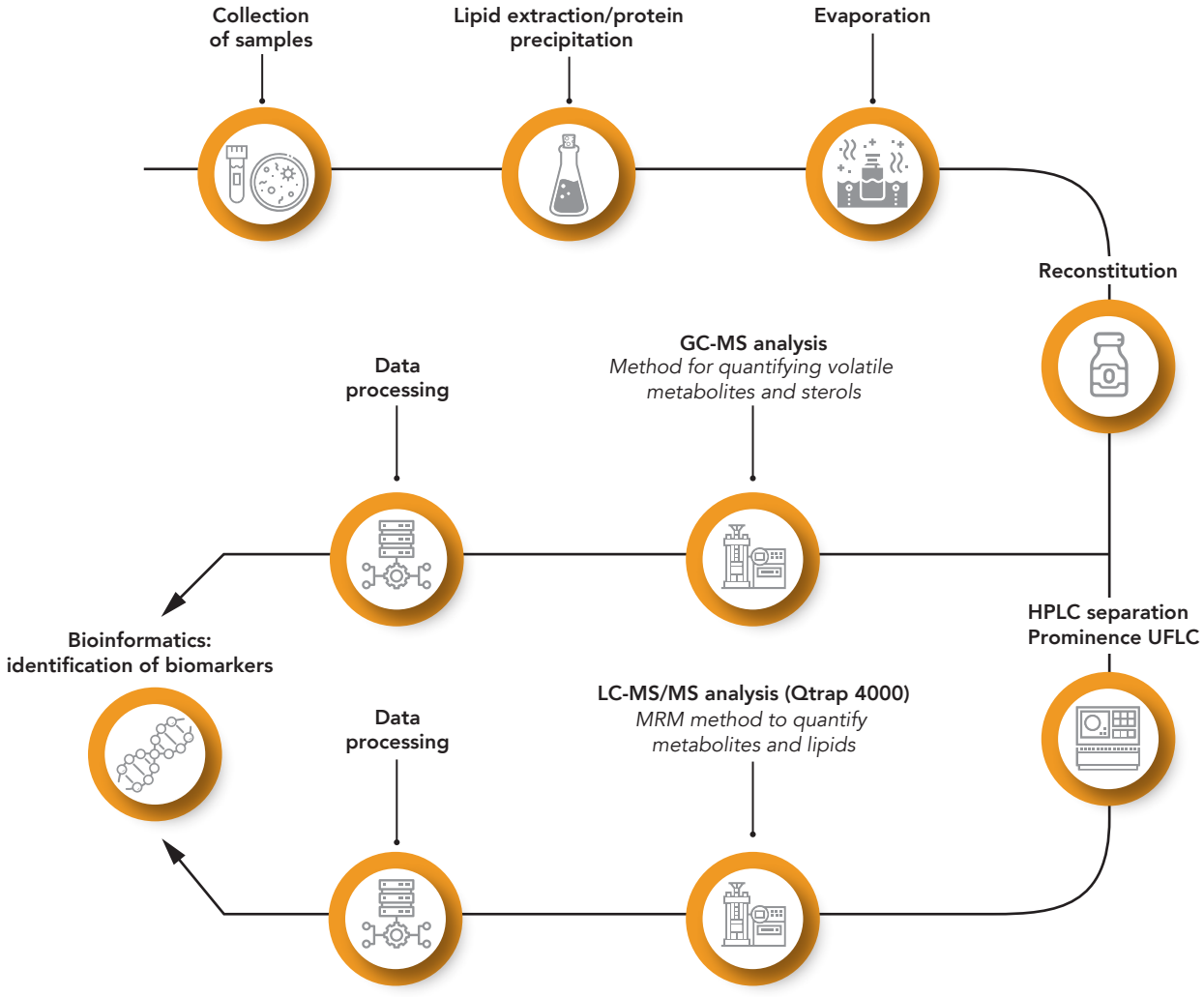
Marie LHOMME
Manager, lipidomics platform

Farid ICHOU
Manager, metabolomics platform

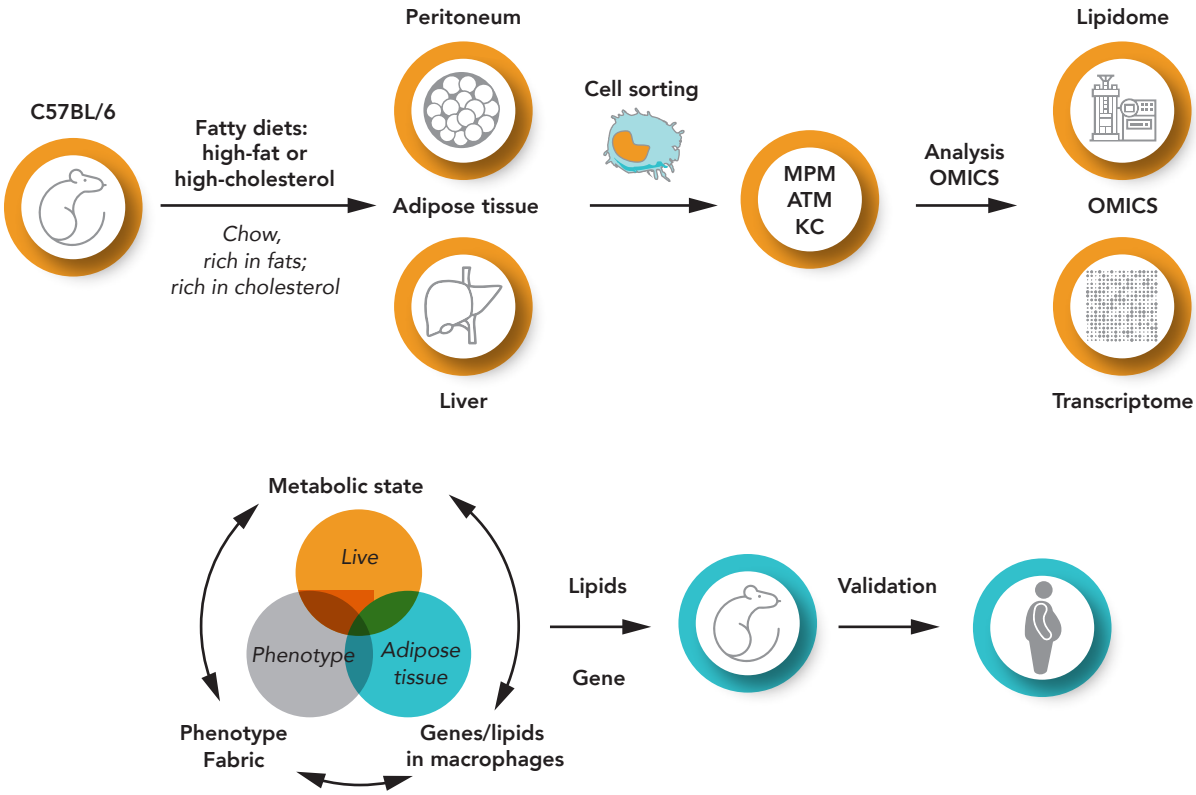
In the field of Big Data, after genomics and proteomics, metabolomics and lipidomics he study of all the molecules linked to the metabolisms and lipid composition of organs and plasma, have appeared. Many studies have shown that this molecular signature changes during cardiometabolic diseases and can be used as a biomarker or therapeutic target. One example is the link between serum lipid profile and the risk of progression of atherosclerosis in the arteries.

Many factors can modify this metabolic and lipid signature, such as gender, body composition, age and lifestyle, which makes it difficult to study. The HUI-ICAN has developed innovative holistic approaches to screen a wide range of molecules, from highly polar metabolites to highly apolar lipids, using a combination of chromatography (liquid or

METABOLOMIC/LIPIDOMIC ANALYTICAL PROCESS



METAMACS PROJECT:
ROLE OF TISSUE MACROPHAGES IN LIPID-RELATED METABOLIC DISEASES



gas) coupled with mass spectrometry technology (LC-HRMS, LC-MS/MS and GC-MS). For data integration and analysis, a dedicated multi-omics integration method called DIABLO was set up, to discriminate between different metabolic phenotypes.

Thus, three types of studies have been developed: (i) global metabolomic analysis for the discovery of new biomarkers (LC-HRMS), (ii) complex lipid profiling (LC-MS/MS), and (iii) targeted approaches for specific metabolic pathways (LC-MS/MS and GC-MS). These methods have been validated many biological matrices (plasma, tissue, faeces, bacteria, cells, intracellular compartments, etc.).

This methodology was used in the integrative and multidimensional MetaMacs project. As a matter of a fact, transcriptomic, metabolomic/lipidomic and phenotyping data were collected from several compartments (liver tissue, adipose and peritoneum tissue), resident macrophages and plasma in obesity and atherosclerosis models.

The metabolomic and lipidomic expertise of the ICANalytics platform has also been applied to study the role of the microbiota in the development of obesity and the metabolism of cholesterol. The team has also studied the changes in insulin sensitivity induced by caloric restriction using an integrative multi-omics approach on different biological compartments (serum, urine and faecal material). Now, thanks to this expertise, the HUI-ICAN teams are tackling the metabolic and lipid plasticity of the encoder and the role it plays in diabetes-related heart disease and atrial fibrillation.

IPS: INNOVATIVE CELLULAR MODELS

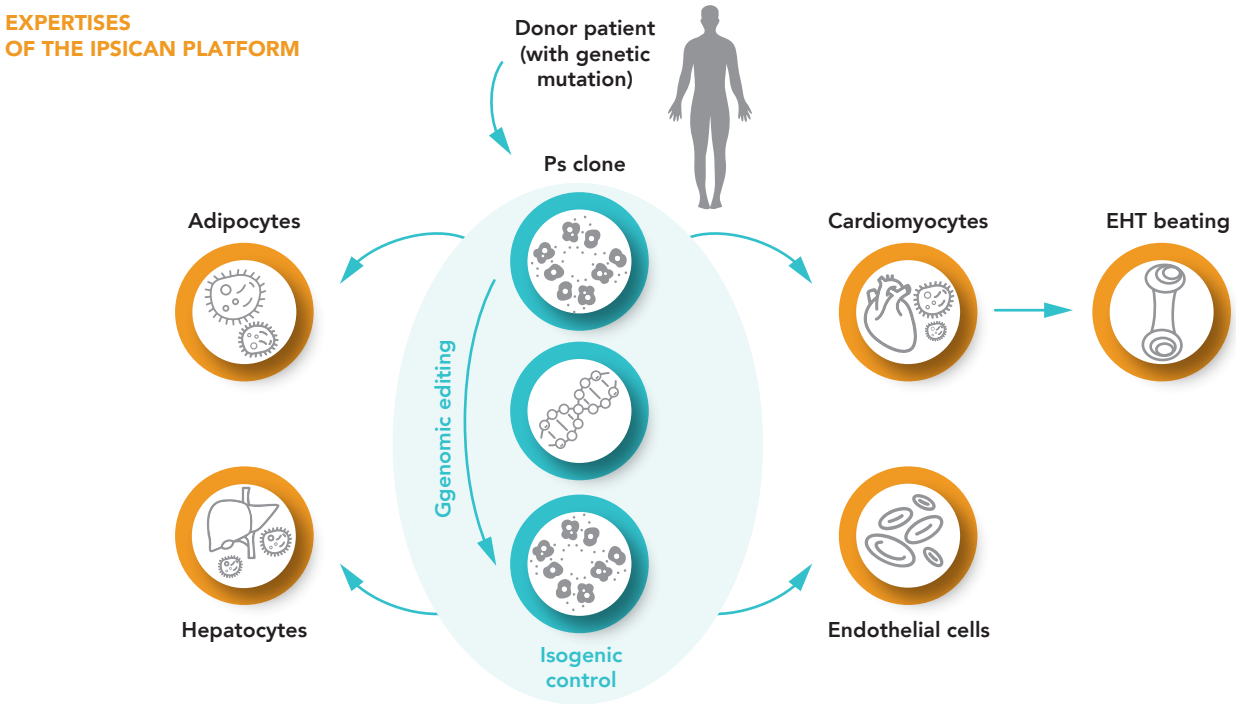
Vincent FONTAINE
Manager, lipidomics platform

The possibility of developing pluripotent stem cells (inducible pluripotent stem cells) from adult cells, in other words cells capable of transforming into other adult cell types, has revolutionised the study of the molecular mechanisms of human diseases. This approach is particularly well adapted to diseases with a genetic origin. In these cases, adult cells, especially blood cells, are taken from sick donors with genetic mutations.

The iPSICAN platform specialises in the production and genetic modification of iPS cells - called genome editing - and their transformation into highly differentiated cells such as cardiomyocytes, endothelial cells, adipocytes, hepatocytes and intestinal cells. Pseudo-tissues, called organoids, are generated *in vitro* to form beating heart muscle or intestinal crypts. To make a cardiac organoid, cardiomyocytes are included in a mixture of hydrogel and fibrin. This cardiac organoid will allow implementation of complex interactions between these cells, and the ability thereafter to study certain physiological parameters such as action potential and heart rate.

iPSICAN also manages the generation of genetically modified iPS clones (iPSc) using Crispr/CAS9 technology, which allows the insertion of corrective matrices into the genome to remove a mutation and thus to generate isogenic clones with the same genetic background as the mutated control clone.

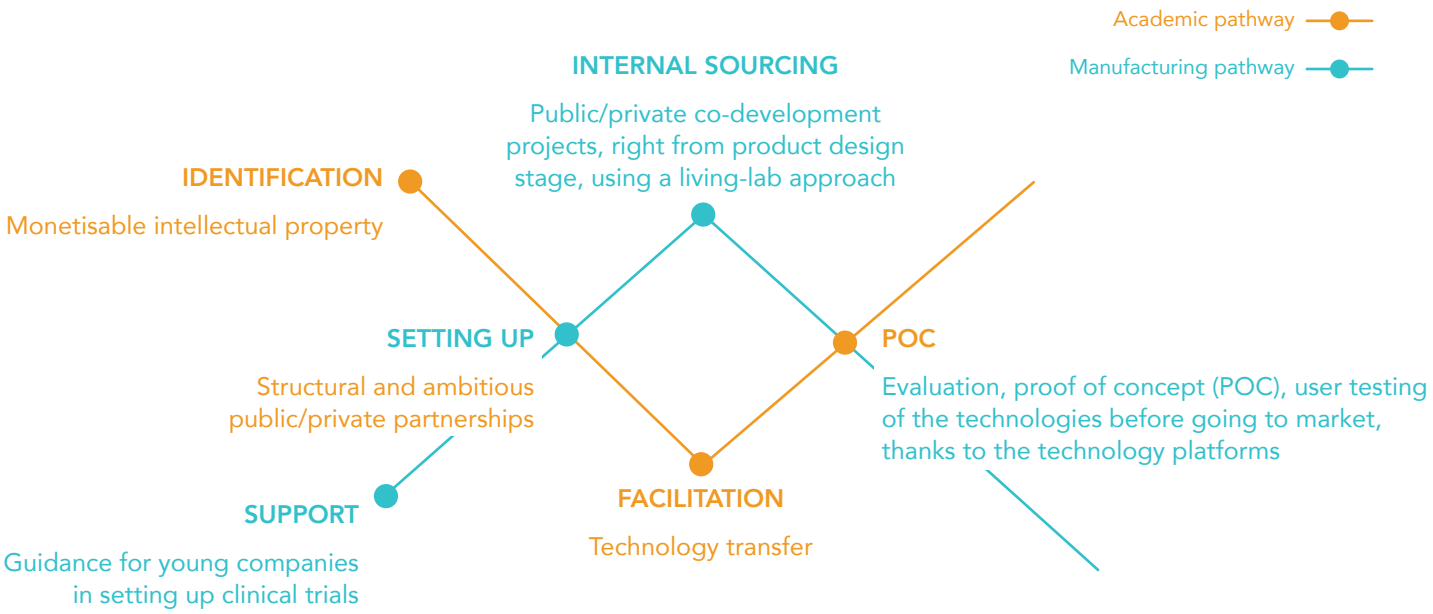
The clinical study called "iPS-CARDIOGEN", involving genotyped hypertrophic cardiomyopathy families, served as the basis for establishing a collection of iPSc lines from patients suffering from cardiomyopathy. In collaboration with the SANOFI laboratory, ICAN-iPS has established isogenic control lines using genome editing, reverted for a causal mutation of the gene coding for cardiac myosin (MYH7) (Fontaine et al. Stem Cell report, 2021).



PARTNERSHIPS

ICAN, THE LINK BETWEEN
ACADEMIC AND MANUFACTURING PARTNERS

Thanks to its integrated approach over the 2018-2020 period, the HUI-ICAN has put in place all the necessary synergies for its partnership project, which is structured on the identification of innovation and the concretisation of partnerships. The year 2019 was marked by the implementation of a 360° approach to partnerships with the ICAN, with a flexible offer that is agile to different needs. The multi-faceted offer ranges from co-innovation to support for the development of products in alignment with the needs of the market and their integration into innovative treatment plans.



RESEARCH SUPPORT SYNERGIES

The speeding-up of partnerships is made possible thanks to the integration of two of the HUI-ICAN's strategic divisions: the scientific operations division and the legal and development division; the HUI also benefits from the expertise of its founders (Sorbonne University, INSERM, AP-HP).

HUI-TRACK

The ICAN was the first UHI to implement a regulatory fast track with the CRU (Clinical Research Unit) at Pitié-Salpêtrière. Coordinated by a CRU-DRCI head of projects, dedicated its scientific community's projects, the validation of regulatory dossiers is thus accelerated and the setting up is done in collaboration between ICAN and the CRU.

ONE-STOP-SHOP

The HUI-ICAN has created "a one-stop-shop" for R&D projects, opening the doors to every type of expertise. The ICAN facilitates access to its expertise, technologies and internal community. Thus, the HUI is simplifying the contractual processes for academically promoted trials and the use of its clinical research platform, thus saving precious time for all its partners.

SPOTLIGHT ON THE CORWAVE PARTNERSHIP

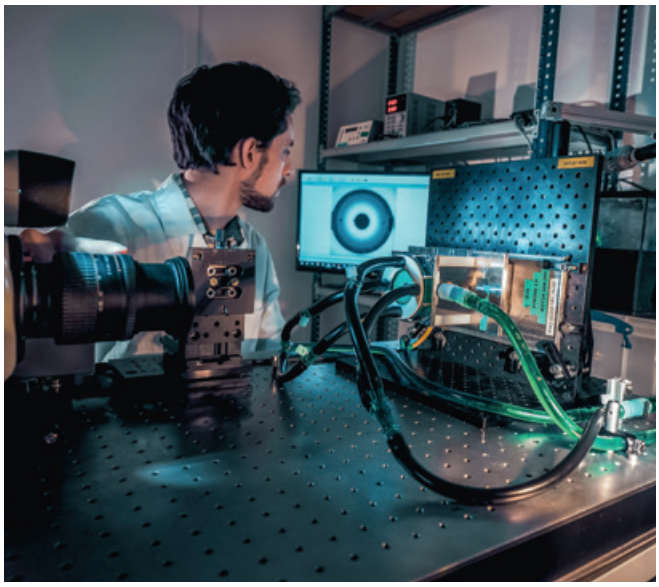
This 360° approach to the construction of projects is perfectly illustrated by the construction of the CALYPSO programme led CorWave

CorWave is a French high-tech company that develops innovative implantable heart pumps, using a breakthrough technology: the undulating membrane. This patented technology, inspired by nature, is able to reproduce a pulse and blood flow rates similar to those of a healthy heart, aimed at reducing the risk of complications associated with the current pumps.

CorWave has therefore chosen to work with major players in the cardiac field such as the Pitié-Salpêtrière Hospital (AP-HP), the Institute of Cardiometabolism and Nutrition (ICAN) and the Lille RUH.

The CALYPSO programme aims to optimise and then clinically validate the CorWave LVAD device developed by CorWave thanks to the highly specialised cardiology expertise of health professionals from the AP-HP and members of the HUI-ICAN community. The ICAN teams bring to CALYPSO the expertise necessary for the analysis of inflammation in cytometry and chromatography, as well as the data produced by current pumps, in order to study all the interactions that can influence the functioning of implantable pumps and cause adverse reactions.

The CALYPSO programme should make it possible to validate this state-of-the-art technology, to be able to respond to people with heart failure who develop complications following the implantation of heart pumps. The CALYPSO consortium is dedicated to placing its members in leading positions in the field of terminal heart failure treatment.



LOUIS DE LILLERS
EXECUTIVE DIRECTOR OF CORWAVE

"ICAN's expertise has been requested for the PSPC CALYPSO. It has a central role in the setting up of the clinical studies that will give us important information with which to optimise our product before it's made available to patients. The ultimate goal is to save patients with advanced heart disease, and to give them the most normal life possible"

SPOTLIGHT ON OUR PARTNERSHIP WITH SIEMENS HEALTHINEERS

Siemens Healthineers wants to foster scientific and medical innovation to support the development of precision medicine and the transformation of treatment plans.

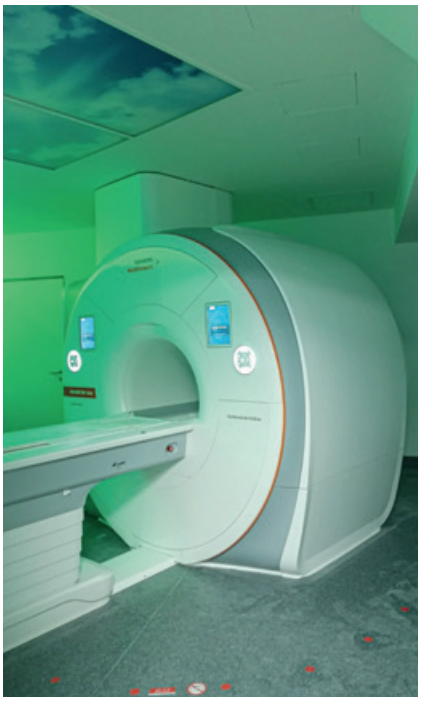
SIEMENS Healthineers wanted to collaborate with the ICAN teams to support the development of the cardiovascular imaging sector. By making human and technological resources available to the ICAN teams for 5 years in order to create synergies between their expertise.

In particular, thanks to "*Compressed Sensing*" technology, SIEMENS Healthineers is working with the HUI teams to develop new, faster image acquisition sequences to improve patient comfort during MRI examinations (reducing the time spent in the machine and the number of captures required to obtain good-quality cardiac images, which will enable more elderly patients to benefit from this type of effective examination.

The teams are also working on improving digital cardiac twin models used in the preparation of interventions, to improve multidisciplinary medical decision-making.

Medical imaging Medical imaging has an increasingly important position in the health sector. Advances in imaging techniques now make it possible to detect diseases earlier and more accurately, for more targeted, less invasive treatment and close monitoring of the therapeutic response. To go further, ICAN has chosen to invest significantly in this field with the acquisition of a state-of-the-art MRI dedicated entirely to human imaging research. This ambitious choice will boost research in cardiometabolic imaging. One of the biggest challenges in cardiac imaging is obtaining good quality images of a constantly moving organ.

The association with SIEMENS Healthineers is an additional asset in developing innovative work in cardiometabolic imaging for the benefit of patients.



AGNÈS MALGOUYRES,
MANAGER, ARTIFICIAL INTELLIGENCE, SIEMENS HEALTHINEERS, FRANCE

Siemens Healthineers was chosen by the HUI-ICAN to equip its "ICAN Imaging Core Lab" platform with the Magnetom SOLA MRI, operational since the start of 2020.

Beyond the installation of this system, the HUI-ICAN and Siemens Healthineers together would like to build genuine clinical-scientific partnership. Based on the complementary nature of the medical expertise of the HUI-ICAN and the technological competence of Siemens Healthineers, this partnership concretised in 2020 through two successful applications to two European calls for projects: EIT Health and Horizon 2020.

The first project, CMRAI (EIT HEALTH) is dedicated to pathologies of the aorta, currently under-diagnosed, for which Siemens Healthineers is going to develop techniques for the ultra-fast MRI data acquisition.

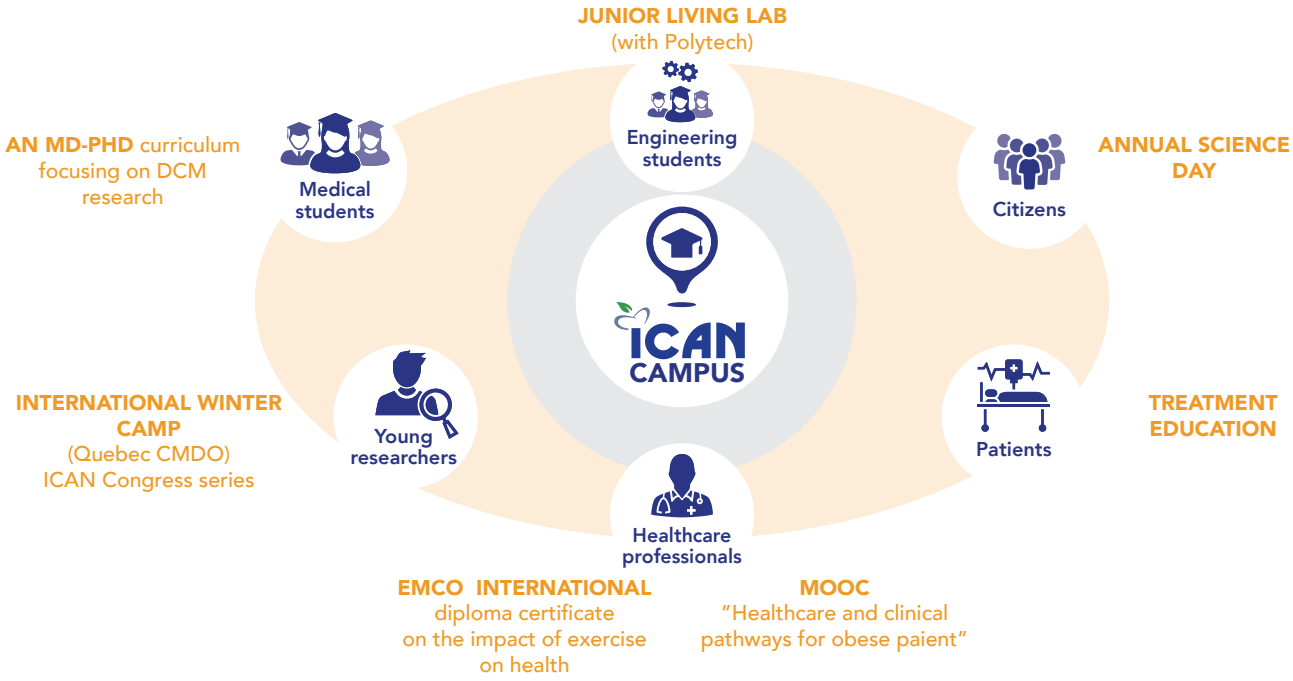
Le second projet, MAESTRIA (Horizon 2020), aims to build and validate the first digital integrative diagnostic platform for atrial cardiomyopathy. It will involve the construction and development by Siemens Healthineers of a *Digital Twin* of the cardiac atria. This work follows the already operational development of a digital twin of the ventricles.

Siemens Healthineers is proud to work alongside Prs. Stéphane Hatem and Alban Redheuil in such an innovative and promising context. This partnership also illustrates Siemens Healthineers' desire to prepare for tomorrow's healthcare, today.

TRAINING

ICAN
CAMPUS

Sharing knowledge with the scientific and medical community, and also with the general public, is an integral part of the HUI-ICAN's mission. A better understanding of cardiometabolic diseases and the progress made in the treatment of these diseases, means it is essential that this new health expertise is rapidly disseminated, to improve patients' treatment and care and their quality of life. Actually, the decompartmentalisation of disciplines and technological progress are forcing us to rethink the organisation of treatment and care for patients with cardiometabolic diseases and severe nutrition disorders.
The HUI-ICAN uses very practical tools to transmit scientific and medical knowledge and to encourage collaborative partnerships.



MOOC

In 2018 Dr Judith Aron and Pr. Jean-Michel Oppert created the first MOOC (*Massive Open Online Course*, dedicated to the care and treatment of people with obesity. It is particularly aimed at doctors and healthcare workers who look after these patients (physiotherapists, dieticians, surgeons, homecare nurses, and also gynaecologists, for example), both as an initial and continual training.

These key messages, presented in the form of vignettes that last a few minutes, are delivered to the learners, who then meet to discuss them amongst themselves, together with the doctor in charge to answer course-related questions.
The purpose of this system is to support healthcare professionals with the care and treatment of their obese patients, which goal has been achieved, given that from among the users of the MOOC :

- 60% confirmed that they learned something
- 30% changed their opinion on obesity
- 10% wanted to deepen their knowledge further

JUNIOR LIVING LAB

ICAN works with engineering students from POLYTECH Sorbonne and Master 1 SESI as part of their second semester internship project, the objective of which is to offer answers to the medical challenges that the ICAN community clinicians meet in their daily practice. This collaborative work puts ICAN's scientific and clinical expertise and the expertise of the engineering students at the service of patients, in order to improve their quality of life. These projects, which are governed by the academic calendar, are very stimulating for the students, who work on very concrete devices that could change the lives of patients.

2018/2019

• An offloading shoe is in development

A prototype for a smart offloading shoe for patients suffering from foot wounds, a serious complication of diabetes, was designed by the Polytech students. The aim of such a project is to improve current medical devices by providing a discreet way of signalling to the patient that they are applying pressure to their wound. As a matter of fact, Dr Georges Ha Van, an expert practitioner of diabetic foot, who works in Professor Hartemann's diabetology department, is sure that the cause of these wounds is mechanical, and therefore that rigorous observance of pressure suppression allows for healing. However, these patients do not feel pain from these wounds because of the neuropathy they also suffer from. Consequently, they are not alerted to the deterioration of their wounds, which sometimes leads to dramatic situations, including amputation. Finding new ways to care for and treat diabetic foot is a major challenge in significantly improving patients' quality of life.

• Detecting daytime sleepiness

Daytime sleepiness is a significant and little-known symptom of sleep apnoea, pathologically frequent in overweight people. Sleep apnoea is very expensive to diagnose because it often requires an overnight stay in hospital (or the loan of a complex appliance) for it to be formally identified. Clinical questioning to identify the risk in patients could therefore be complemented by a device capable of detecting daytime sleepiness, which patients are not always aware of despite their dangerous nature, most particularly when driving. Work on daytime sleepiness is continuing between researchers at Sorbonne University, clinicians from the "respiration, resuscitation, rehabilitation, sleep" department (R3S) and endocrinologists from the ICAN community.

In 2019/2020

• Detecting muscle cramps in patients on statins

Leg pain is a common reason why cholesterol-lowering statin therapy is stopped. Statin therapy is one of the primary treatments for atherosclerosis of the arteries, although such pain is not always attributable to that treatment. The HUI-ICAN teams and POLYTECH students worked together on a prototype of an innovative, portable, non-invasive device capable of detecting muscle cramps and/or painful contractions in patients reporting muscle pain. It falls within the context of telemedicine solutions based on the smart evaluation of large amounts of data collected by sensors and analysed using methods of artificial intelligence (AI).

ICAN
THE CMDO NETWORK

CMDO
Réseau de recherche en santé cardiométabolique, diabète et obésité

Since 2014, ICAN has established strong links with the Quebec Research Network on Cardiometabolic Health, Diabetes and Obesity (CMDO) with the objective of creating a strategic and sustainable partnership between France and Quebec on research training in the field of cardiometabolic health, diabetes and obesity. This transatlantic programme allows young research professionals from the HUI-ICAN and all Quebecois universities to work together on Canadian soil each year.

These inter-university gatherings stimulate collaboration between transatlantic laboratories. Meetings at scientific conferences (ICAN series and CMDO scientific meetings) increase the influence and scope of everyone's work and stimulate collaborations.

Winter CAMP

The winter camp, which takes place every year in February (not including during the recent health crisis), provides a week of intensive training in interactive workshops with internationally renowned speakers.

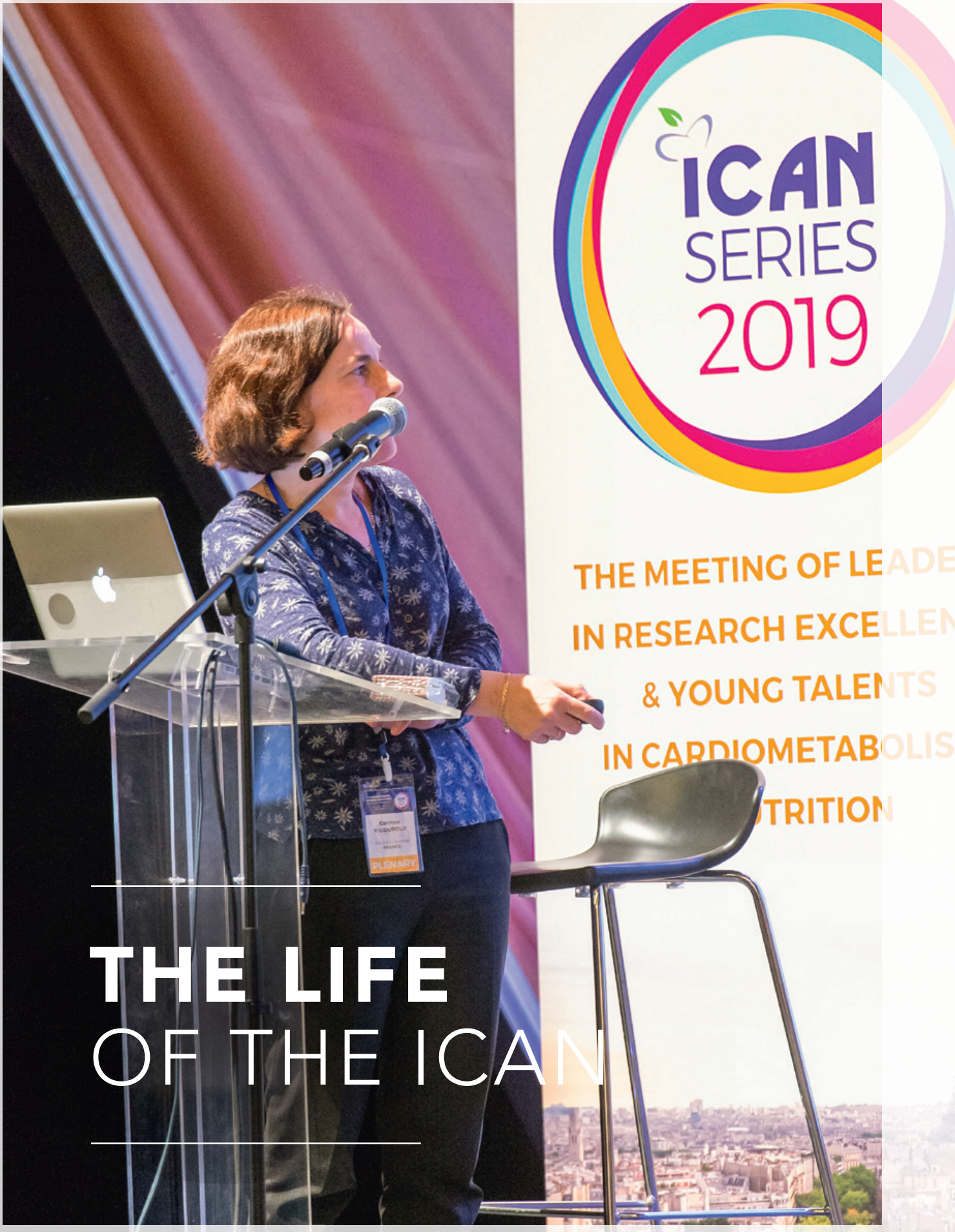
Thanks to the precious moments of conviviality it offers, the winter camp is a privileged space for networking, which opens up new postdoctoral opportunities for participants across the Atlantic in the field of foundational, clinical and epidemiological research in cardiometabolic health.

PROF. ANDRÉ CARPENTIER
DIRECTOR THE CMDO NETWORK

LUCIEN JUNIOR BERGERON, PHD
DEPUTY DIRECTOR THE CMDO NETWORK

Since 2014, the CMDO community has had the privilege of welcoming the next generation of scientists from France (ICAN) through a student exchange that extends far beyond knowledge transfer. During the activities surrounding the winter camp, one of the flagship activities of our network, friendships are made, leading in some instances to sustained scientific collaborations that can have an incredible leverage CMDO research internationally. This Francophone week in Quebec is often a high point for our campers, whether they are from France or Quebec, combining a cultural experience with first-class, multidisciplinary scientific immersion. Long may this student exchange live, for the benefit of international research at CMDO.

FOR INFORMATION ON THE CMDO NETWORK: lucien.junior.bergeron@rrcmdo.ca



THE LIFE OF THE ICAN

EVENTS
HIGHLIGHTS

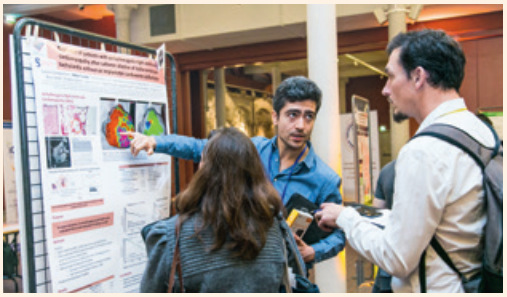
ICAN SERIES

A unique, international congress

The HUI-ICAN organises this unique international congress once a year. It is dedicated to cardiometabolic and nutrition diseases. Thanks to top-level interventions, this is now an unmissable event in the research landscape calendar.

In 2019, the sixth version of the ICAN Series had the theme of "Cardiometabolic disease interfaces: creating new paradigms". The ICAN Series has brought together world-renowned speakers in foundational and clinical research, and young researchers, in a splendid venue: "The Palace with the Golden Door".

This series of conferences only started six years ago, but thanks to dedicated academics, it has quickly become an institution in the field of cardiometabolic and nutrition-related disorders. The presentations have been both fascinating and engaging, prompting interesting discussions between our research groups and the conference participants.



Poster presentation of young researchers.

Prize giving to the young researchers.

Speech by Xavier Prieur, lecturer at the Université de Nantes [University of Nantes].

ROUND TABLE

Academic and manufacturing research confronting new challenges

HUI-ICAN, in partnership with Medicen, organised a symposium with the principle academic and manufacturing opinion leaders.

The aim of the symposium was to determine whether recent discoveries could be exploited, and to create new interactions to help industry leaders identify the next wave of innovative and pertinent solutions for cardiometabolic diseases.

Organised as a round table, industry leaders such as Servier, AztraZeneca, Siemens and Sanofi were able to exchange views with the top leading specialists in cardiometabolism.

With more than 150 listeners, this event was a real success for all the speakers and participants, and was a catalyst for the start of some promising partnerships.

LA PARISIENNE [THE PARISIAN]

Every year the HUI-ICAN is one of the 300 enterprises that participate in the La Parisienne race.

It's an opportunity for the participants to share really great times together, between the preparation picnic and the day of the race.

A unique opportunity to meet and share in a space that mixes sport, health and festivities.

COV ICAN
THE FIRST HUI-ICAN FUNDRAISING CAMPAIGN

COV·ICAN
CAMPAGNE D'URGENCE

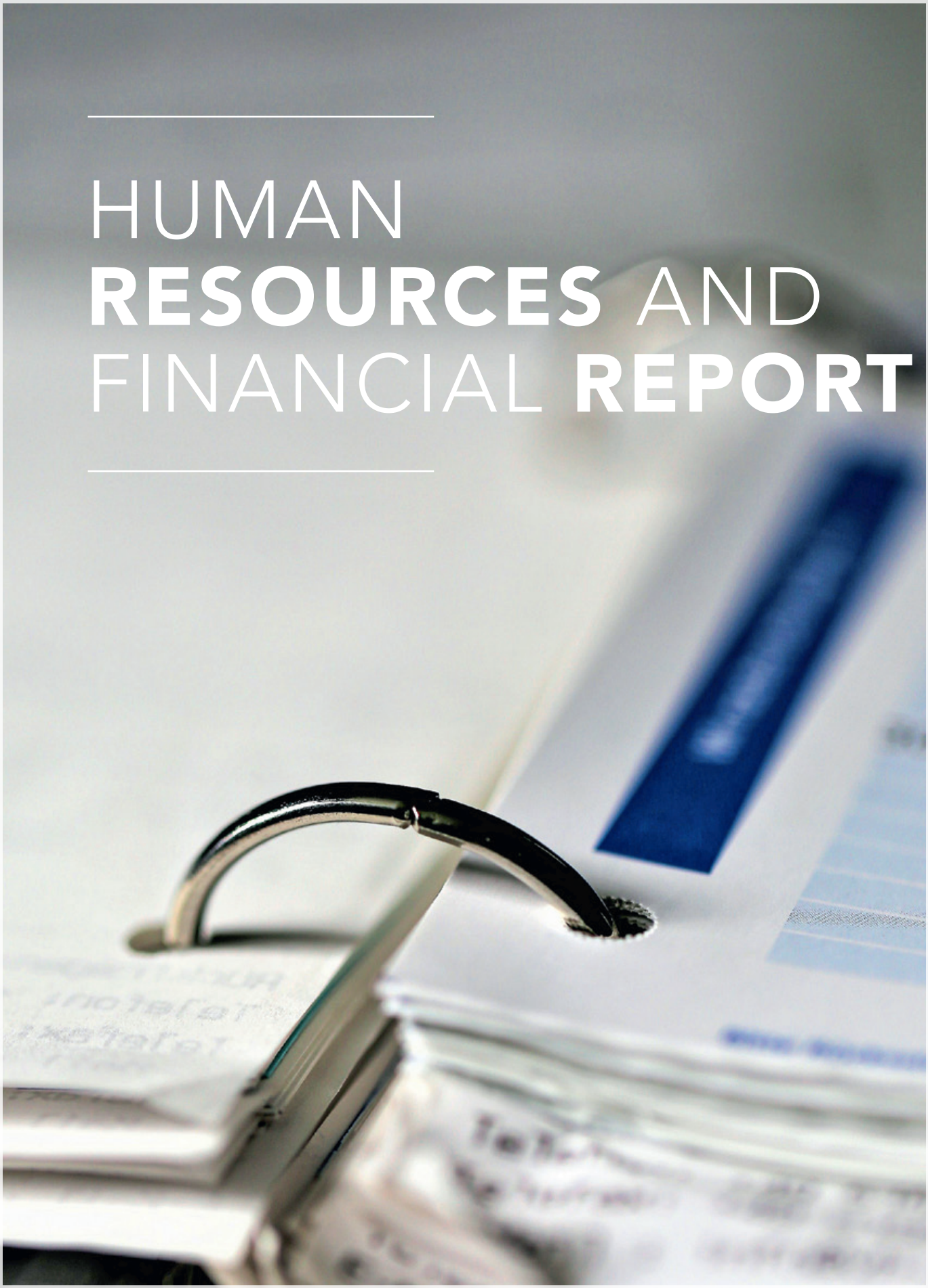
To accelerate research innovation for the benefit of people with cardiometabolic diseases, the HUI-ICAN wanted to appeal to the public's generosity to expand its private resources. And now it's a done deal! The COVID-19 crisis actually ended up accelerating the process The HUI-ICAN launched its first fundraising campaign in August 2020, to finance innovative research programmes to combat COVID-19.

As a matter of fact, people with long-term diseases (diabetes, obesity, cardiovascular diseases etc.) are at increased risk of developing the more severe forms of COVID-19. So the teams of doctors and researchers at ICAN mobilised quickly to launch research programmes to better understand the interactions between COVID-19 and cardiometabolic diseases. This campaign raised the public profile of the HUI-ICAN as a fundraiser.

The donations collected contribute to financing the COVID_CT project led by Pr. Alban Redheuil. This project aims to better understand the risk factors for severe forms of Covid-19 and to reduce the number of deaths, by analysing imaging data and using artificial intelligence to create predictive algorithms.

The ICAN would like to thank its historical sponsors for their essential support of the research conducted by the Institute's teams

BIOTRONIK excellence for life
Boston Scientific Advancing science for life™
Medtronic



HUMAN **RESOURCES** AND FINANCIAL **REPORT**

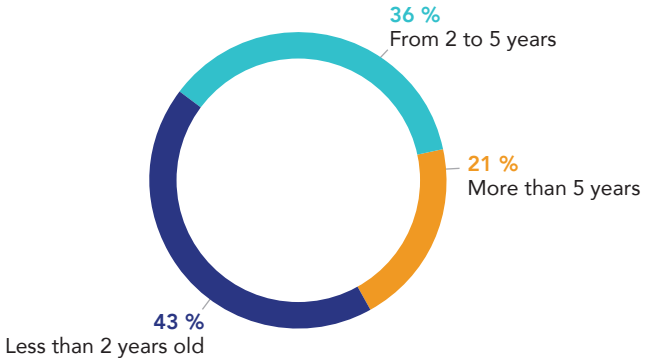
ICAN
HUMAN RESOURCES 2020

44
ICAN SALARIES

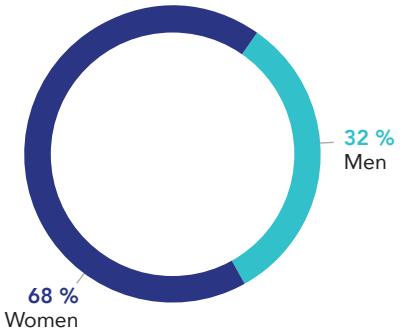
68%
WOMEN

32%
MEN

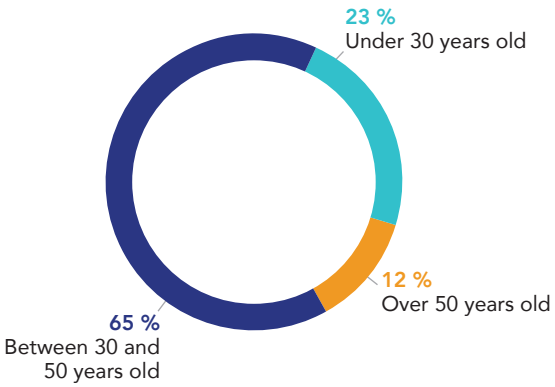
WORKFORCE BY **LENGTH OF SERVICE**



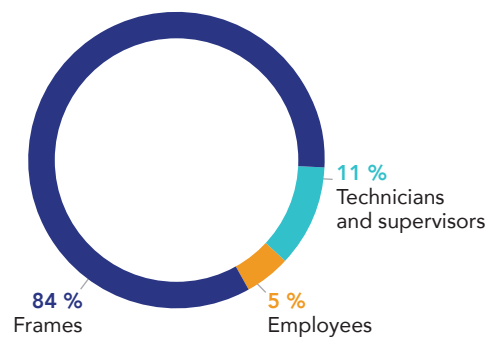
BREAKDOWN **OF HIRING BY CONTRACT AND SEX**



WORKFORCE BY **AGE**



HIRES **BY CONTRACT**



Faced with the challenge of defining an economic model aiming for financial autonomy more quickly than the other UHIs, an in-depth review has been carried out over the past two years, the core missions of the UHI. This helped identify a clear direction for the future: ICAN must continue to refocus on its added value as a shared and fluid gateway for the scientific offerings of its community of doctors and researchers, for the economic players.
This is the context in which our financial management policy is evolving. Manufacturing, European and international collaborations have been developed and the volume of services provided by ICAN's biology platforms is increasing.

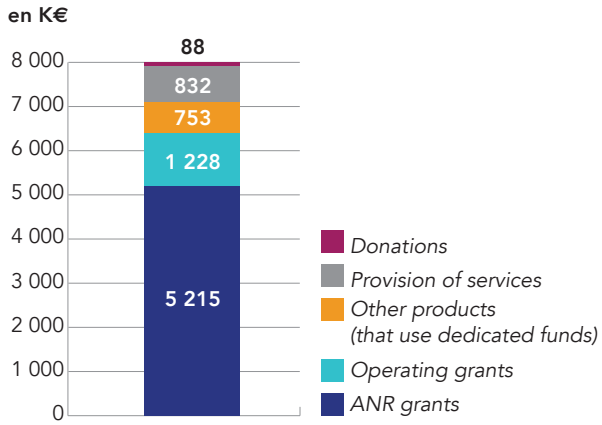
Stéphanie Lapous
Administrative and Financial Manager

INCOME STATEMENT **2018 - 2020**

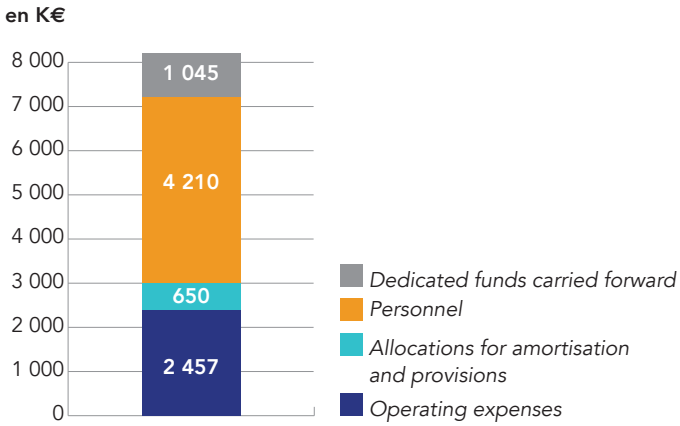
INCOME STATEMENT IN K€	2018	2019	2020
Provision of services	831 063	1 501 479	1 363 462
Operating grants	1 228 273	703 593	869 880
Donations	88 000	71 000	99 858
ANR grants	5 215 288	2 083 062	4 640 211
Other products (that use dedicated funds)	753 420	975 319	976 486
TOTAL OPERATING INCOME	**8 116 044**	**5 334 453**	**7 949 897**
Operating expenses	(2 457 080)	(2 093 480)	(1 605 475)
Allocations for amortisation and provisions	(650 289)	(539 330)	(672 472)
Personnel	(4 210 264)	(4 224 996)	(2 989 132)
Dedicated funds carried forward	(1 045 362)	(766 320)	(2 628 900)
TOTAL OPERATING EXPENSES	**(8 362 995)**	**(7 624 126)**	**(7 895 979)**
OPERATING PROFIT/LOSS	**(246 951)**	**(2 289 673)**	**53 918**
Financial profit/loss	59 843	25 028	5 497
Financial income	59 843	25 675	5 497
Financial expenses	-	(647)	-
Pre-tax profit/loss	(187 108)	(2 264 645)	59 415
Exceptional income	3 204 870	41 436	196 940
Exceptional expenses	(523 452)	(212 836)	(1 500)
Exceptional profit/loss	2 681 418	(171 400)	195 440
TOTALS			
TOTAL INCOME	**11 380 757**	**5 401 564**	**8 152 334**
TOTAL EXPENSES	**(8 886 447)**	**(7 837 609)**	**(7 897 479)**
NET PROFIT/LOSS	**2 494 310**	**(2 436 045)**	**254 856**

It should be noted that the financial year 2018 ended with a significant surplus of €.2.5m This result was achieved as the consequence of exceptional income of €2.7 million, due to an accounting adjustment. A change in the ANR's financial regulations increased the management fee charged to the UHI from 4% to 8%. This exceptional income is offset in the 2019 financial year by a lower declaration of eligible costs to the ANR, leading to a negative result for that year.

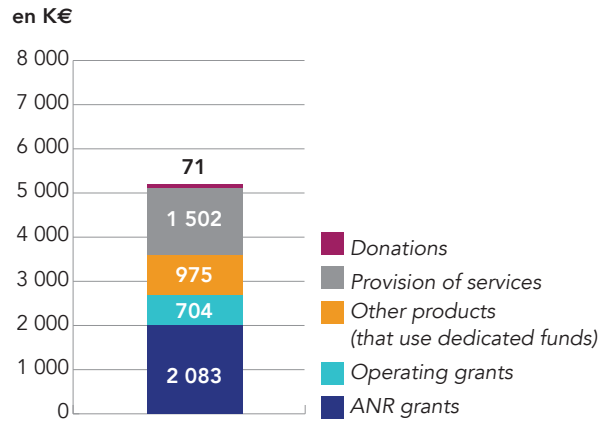
TOTAL OPERATING INCOME 2018
8 116 K€



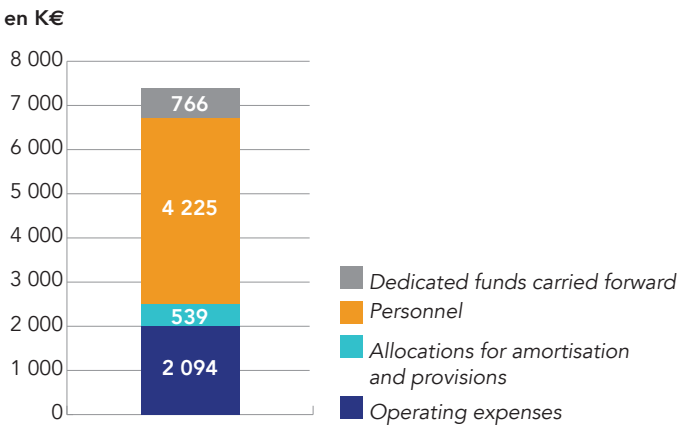
TOTAL OPERATING EXPENSES 2018
8 362 K€



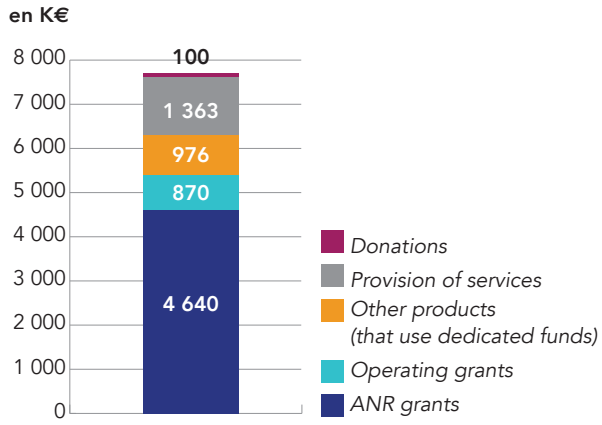
TOTAL OPERATING INCOME 2019
5 335 K€



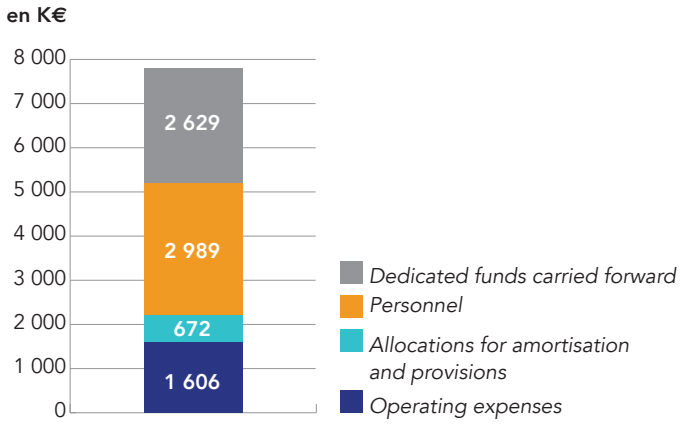
TOTAL OPERATING EXPENSES 2019
7 624 K€



TOTAL OPERATING INCOME 2020
7 949 K€

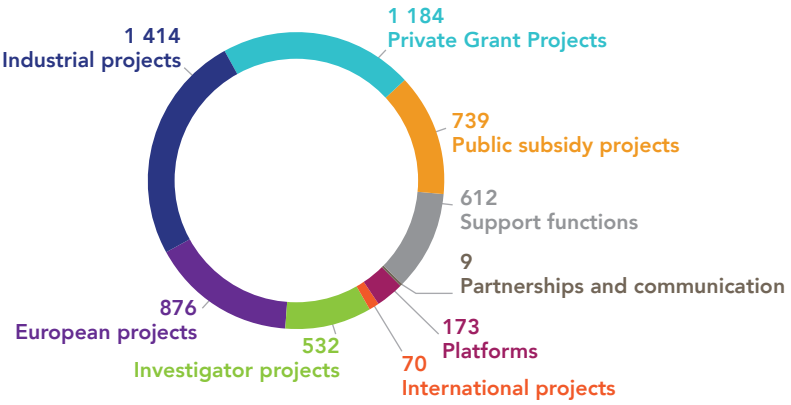


TOTAL OPERATING EXPENSES 2020
7 896 K€



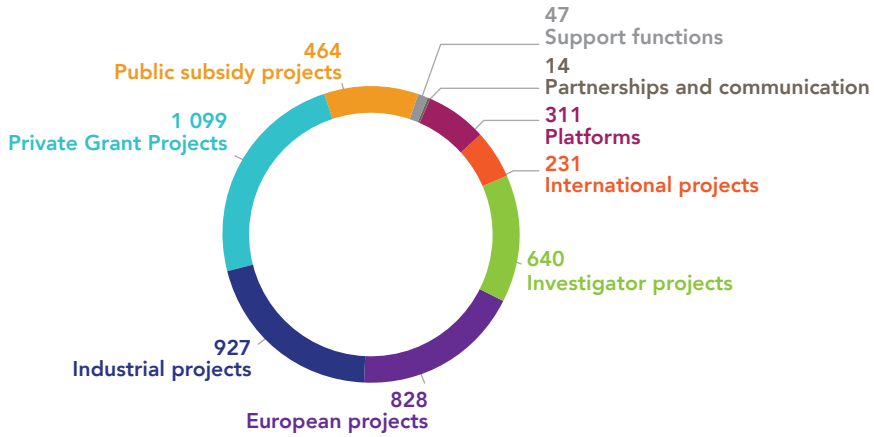
RESOURCES BY PROJECT TYPE 2018

5 609 K€



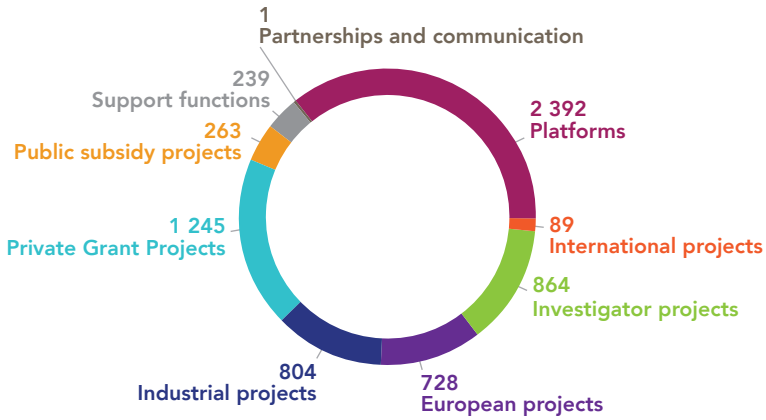
RESOURCES BY PROJECT TYPE 2019

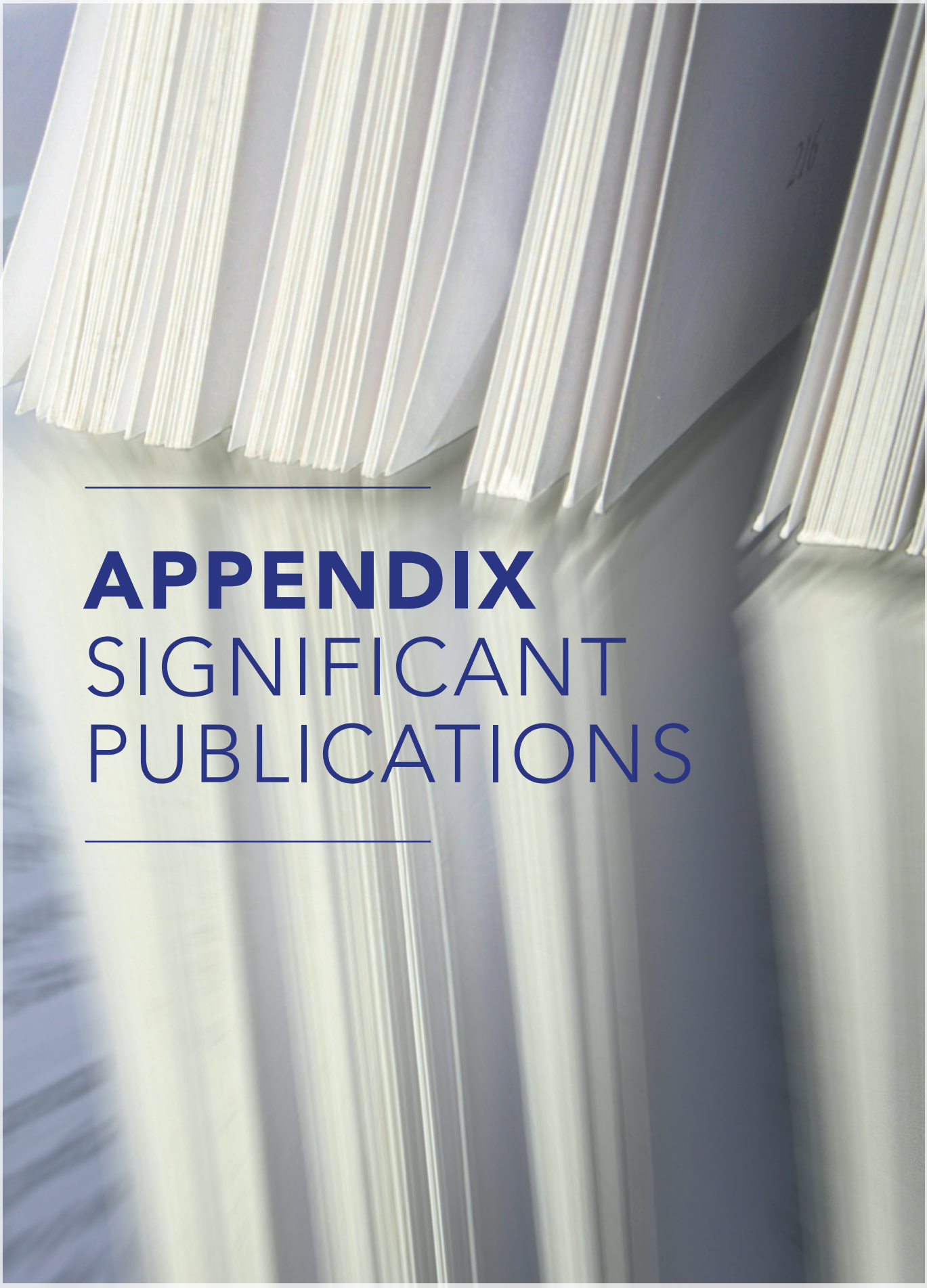
4 561 K€



RESOURCES BY PROJECT TYPE 2020

6 625 K€





APPENDIX
SIGNIFICANT PUBLICATIONS

SIGNIFICANT PUBLICATIONS 2018 - ANR REPORT

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Hôpital de la Pitié-Salpêtrière
47-83, boulevard de l'Hôpital - 75013 Paris
Pavillon Claude Bernard
communication@ican-institute.org