Activity Report 2021

IHU ican

Foundation for Innovation in Cardiometabolism and Nutrition

OVERVIEW

The IHU ICAN

CROSSED VIEWPOINTS

Stéphane Hatem
Chief Executive

Stéphane BARRITAULT
General Secretary

What would your assessment be of 2021 for the IHU ICAN?

STÉPHANE HATEM 2021 was a pivotal year for the IHU ICAN. The launch of major European projects: MAESTRIA, CMR AI, which leverage the IHU ICAN's know-how and expertise, have committed it to the strategic areas of Big Data, AI, imaging, dialogue between organs and new care pathways. Today, the IHU ICAN is centred on transversal scientific projects that mobilise the teams on both operational and scientific aspects.

> **THE LAUNCH OF SIGNIFICANT EUROPEAN PROJECTS THAT DRAW FROM THE ENTIRETY OF ICAN'S KNOW-HOW AND EXPERTISE."**
>
> Stéphane Hatem

The IHU's challenging period is now behind us. In 2021, our new General Secretary, Stéphane Barritault, concluded the restructuring of the IHU's governance, strengthened the links with our founders and put in place a new financial trajectory. Under his leadership, ICAN has become an active partner in the Alliance of French IHUs, which brings together 6 of the IHU's. This alliance aims to promote the IHU's place as a key players of the "Future Investments" national plan and of "France 2030" healthcare initiative.
In 2021 the IHU was structured around 3 pillars: a united community, structured translational research projects and a strong position in the cardiovascular and metabolic diseases ecosystem. Bolstered by the work accomplished, we can now calmly prepare the evaluation of the 6 IHU created in 2011, that has been announced for 2023.
In 2022, we will continue the work of structuring the IHU and strengthening our relationship with our founders, with the aim of developing ambitious new projects, international partnerships and new treatment pathways.

STÉPHANE BARRITAULT Background work, less visible but nonetheless very important, has been carried out to streamline the internal circuits and give more transparency to the IHU's financial management, in order to establish a very precise analytical follow-up of projects. This work was absolutely essential, given the multiplication of the large-scale projects carried out by the IHU teams.

What were the challenges for the IHU ICAN during the pandemic crisis that extended to 2021, for the medical and science teams?

STÉPHANE HATEM The first big challenge is related to the fact that many of the active members of the IHU, specifically the clinical researchers, were occupied with the treatment and care of covid patients, and the reorientation of hospital activities.

Their reduced availability had an impact on the daily life of the IHU. The second challenge was to be able to support our clinicians and researchers in this very unusual context. To that end, we participated in the submission of scientific projects to advance our understanding of the pathogenesis of SARS-COV-2 infections and to improve the treatment and care of patients, particularly those suffering from cardio-metabolic diseases, diabetes and obesity, who are at greater risk of developing severe forms of COVID-19. Our imaging teams' expertise was instrumental to the implementation of these actions.

STÉPHANE BARRITAULT Like all institutions and organisations, It was necessary to reorganise at every level, with a near-systematic reliance on remote working and online meetings. But in the end the impact was relatively limited because all our staff members stayed very engaged, and the life of the IHU was able to continue.
The pandemic had destabilising effects because, as for everywhere, there was a culture of urgency and immediacy that grew stronger and, at the same time, we faced delays in the launching of some of the non-COVID-19 related projects. The major challenge was to restabilise the processes and the organisation, in the face of this new reality. There was a really substantial and formidable mobilisation of all the IHU teams, who were able to maintain their commitment to projects and activities with determination, despite sometimes a lack of visibility.

ALL STAFF MEMBERS STAYED VERY ENGAGED."

Stéphane Barritault

The IHU ICAN is ranked among the best cardiometabolic research centres, what are its main strengths?

STÉPHANE HATEM The first asset, without doubt, is its community of experts in different fields, which enables a response to the challenges posed by these multi-disciplinary and multi-approach diseases that require a lifetime of treatment and care. They cannot be restricted to one speciality or one or two scientific questions. The IHU ICAN facilitates and accelerates these interactions between teams and disciplines and enables the conception of scientific projects and interdisciplinary treatment plans.

> **"TODAY THE IHU HAS A CHAIN OF EXPERTISE AND KNOW-HOW FOR SETTING UP SCIENTIFIC PROJECTS, FROM THE DESIGN OF THE PROJECT TO IMPLEMENTATION OF STUDIES, INCLUDING THE REGULATORY AND FUNDING ASPECTS."**
>
> Stéphane Hatem

The second asset is the availability of patient cohorts. During our first decade, a huge amount of work was put into structuring cohorts and registers of patients suffering from metabolic diseases, from regulatory aspects all the way to the valorisation of the research. This extremely valuable asset is open to our entire community of clinicians and researchers. It is also thanks to the cohorts that the IHU has initiated and conducted innovative academic and manufacturing projects.

Another asset is our research and technical platforms, which provide unique expertise in human MRI imaging, metabolomic and lipidomic analyses and the reprogramming of somatic cells and organoids, which are open to academic and industrial world. Our ICAN Imaging platform, solely dedicated to human cardiovascular research, is unique in France. Our OMICS lipidomics and metabolomics platform is also a leading platform for cardiometabolism research projects. In 2021 we created the I/O platform for the analysis and integration of multi-omics and clinical data, in response to the growing needs of researchers.

But probably, the greatest asset specific to the IHU ICAN is that it now has a chain of expertise and "savoir-faire" for setting up scientific projects, from the design to the implementation of the studies, including the regulatory and funding aspects. The system allows for a strong coordination and piloting of projects, which are proving to be important for the use of health data and artificial intelligence, the new frontier of the translational biomedical research. Our recent successes, notably European funded public/private partnership projects, fully validate this strategy.

STÉPHANE BARRITAULT When I arrived in April 2021, one of the first strengths I noticed was ICAN's pivotal place in the cardiometabolic research landscape. The IHU's capacity to manage complex projects covering all stages of French clinical and fundamental research, and its ability to obtain funding, makes it an asset for its scientific community. The IHU ICAN, with an excellence in research anchored around a precise theme, can clearly be identified among the players who count in the cardiometabolic field. This visibility and coherence are our community's strengths, and allows for the creation of public/private collaborations, an asset on which our public founders can also rely.

The second strength that I wanted to focus on is the IHU's ability to support the community's projects, to render them more audacious and at times, be able to carry out projects that would not have been able to be structured without the support of the ICAN teams on the regulatory, financial and organisational aspects.

Our size, and the way we work, allows us to be proactive and agile in response to the needs of the researchers and founders. This driving force for acceleration is one of the reasons for the existence of the IHU.

What are the next significant projects and challenges for the IHU ICAN?

STÉPHANE HATEM We are going to expand our new strategic orientations initiated in 2020: to generate and to use of health data, particulary those created by imaging and Omics approaches.
There are two flagship projects of particular note: the first reference atlas for cardiometabolism imaging in France, and the development of healthcare digital twins.
The first project will be carried out with our partner and founder, INSERM (National Institute of Health and Medical Research). This is the first reference atlas of cardiovascular imaging in a French healthy population, and will include young subjects, from 20 years old, which is quite exceptional. A first pilot phase will be entirely undertaken by the IHU at the Pitié Salpêtrière site, then a second phase will enable the atlas to be expanded to a national level.

> **“THIS IS THE FIRST REFERENCE ATLAS OF CARDIOVASCULAR IMAGING IN A HEALTHY POPULATION.”**
>
> Stéphane Hatem

The second challenge to address is to participate in the development of digital health in France, in particular, through digital twin technologies to better predict the physio-pathological processes that lead to cardiometabolic diseases and for precise upstream medicine. This project is led by Dassault Systems, with the participation of 5 other IHU’s. The ambitious project, launched in 2021 to set up the first digital platform to help diagnose atrial fibrillation (H2020 MAESTRIA) will be fully deployed.
All this work by the IHU ICAN should contribute to the emergence of a real sector in cardiovascular and metabolic diseases in France, on which a whole network of manufacturers, biotech, digital and health companies can rely on.
And as for all the others IHU in the first-wave, ICAN will be reevaluated in 2023,

with the allocation of structural funding at stake for all. This means looking to new horizons for the next step in the development of the IHU's scientific projects. For ICAN, This evaluation comes at a time when ICAN has finished consolidating its scientific trajectory, its governance, and its efficiency. All the factors enabling the development of the IHU are now in place and fully deployed. The renewal of the IHU label will take an important strain of ressources on the teams a lot but it remains essential that we stay mobilised on a daily basis to develop the scientific and clinical projects.

STÉPHANE BARRITAULT To accomplish all these projects, to meet the public health challenge that is the fight against cardiometabolic diseases, to ensure that there are sufficient resources to achieve the ambitions that have been set out. This is a crucial challenge for the role out of the IHU ongoing scientific project and for concretising future projects. A second challenge is to structure a quality management system within our IHU, as a leverage to further improv our processes and the way in which we can respond to projects carried out by the community.
The third challenge that I see, is maintaining a viable and sustainable financial trajectory, in order to ensure the development of innovations. In 2021 the IHU initiated a sponsorship strategy to contribute to the financing of its innovations. Sponsorship should become a constant resource for financing projects in the coming years. The issue of renewing the IHU and securing structural funding will guide the financial trajectory of the IHU and how future projects can be implemented.
Another significant hurdle for the teams to overcome is to make metabolic diseases visible. Among the general public, the concept of cardiometabolic diseases (CMD) is still poorly understood. However, CMD's are the primary cause of chronic diseases and responsible for so many deaths in France. New pluridisciplinary, global approaches must be developed to really fight against CMD (diabetes, obesity, cardiovascular disease and NASH).
Thus, in 2021 the IHU ICAN decided to change visual identity, in order to improve its communications and be more visible in matters of public health.
Bringing CMD's to the attention of the general public is essential. Communicating about the interactions between diabetes and obesity, or diabetes and cardiovascular diseases (CVD), and NASH will raise awareness of the severity of these diseases and the importance of research to understand the mechanisms of disease onset and progression, and improve patient treatment and care.
Once again, ICAN is fully committed to its task of raising awareness to prevent CMD's. To work on the visibility of metabolic diseases means working on the primary and secondary prevention of the leading cause of chronic diseases in France.

NEW PLURIDISCIPLINARY, GLOBAL APPROACHES MUST BE DEVELOPED TO REALLY FIGHT AGAINST CMD (DIABETES, OBESITY, CARDIOVASCULAR DISEASE AND NASH).

Stéphane Barritault

KEY FIGURES 2021

A budget of 6 million euros

53 collaborators

FUNDAMENTAL AND APPLIED RESEARCH

221 researchers

11 research teams

7 cutting edge
scientific research platforms

5765 scientific publications
of which 169 have an impact factor > 10

30 patents
in the portfolio

CLINICAL RESEARCH AND TREATMENT

168 doctors

12 clinical teams

1 Clinical Research Platform
specialising in cardiometabolism and nutrition

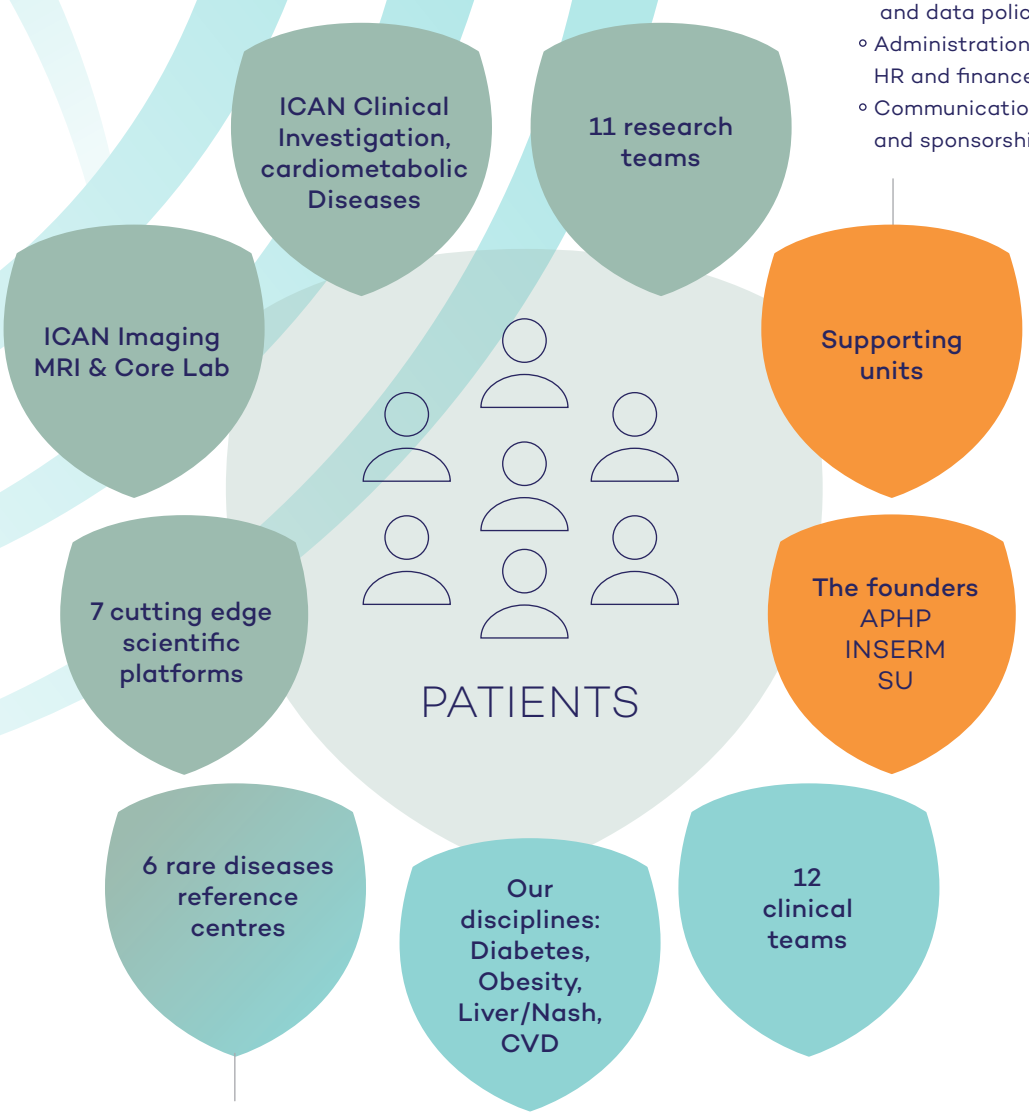
1 Cardiometabolic Imaging Platform
(MRI and Core Lab) dedicated to clinical research

55 clinical studies
underway of which 27 are commercial and 28 are academic

6 reference centres for rare diseases

> THE IHU ECOSYSTEM

The IHU ICAN is located at the heart of the Pitié Salpêtrière hospital group and works in close collaboration with its founding member teams to conduct innovative, high-impact scientific projects.

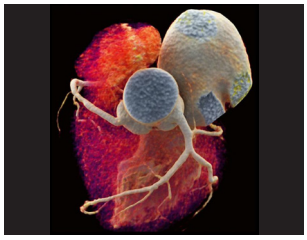


- Innovation and Research Valorisation Unit
- Legal, compliance and data policy Unit
- Administration, HR and finance Unit
- Communication and sponsorship Unit

- Prader-Willi Syndrome and other rare obesities - PRADORT
- Hereditary and Rare Cardiac Diseases
- Rare Insulin-Secretion and Insulin-Sensitive Pathologies
- Inflammatory diseases of the Bile Duct and Auto-immune hepatitis
- Rare Endocrine Growth and Development Diseases
- Rare Gynaecological Diseases

METABOLIC DISEASES

**The global progression of metabolic diseases has not slowed down.
They are the primary cause of chronic diseases.**



Cardiovascular diseases

1st cause of mortality before the age of 65, 17.7 million deaths a year globally, representing 31% of the worldwide mortality rate (all causes included). Women represent 54% of deaths. Cardiometabolic diseases are risk factors for developing severe forms of numerous other diseases, as was the case with Covid-19. To meet these public health challenges, the IHU ICAN is developing an innovative model of translational research that places the new interfaces between organs at the centre of its research: the heart, microbiota, adipose tissue, liver and immune system are very promising avenues for gaining a better understanding of the physiopathological mechanisms of the development of cardiometabolic diseases.

Diabetes

Since 1980 the global prevalence has quadrupled,, 1 person in every 20 in the world is diabetic. It is the 9th cause of death globally (1.5 million deaths a year) and the number of deaths due to diabetes has increased 70% since 2000. In France, more than 3.7 million people take diabetes medication. It's a disease that leads to several complications: blindness, renal insufficiency, lower limb amputation, cardiac insufficiency, etc.

Obesity

On a global scale the number of obese people has tripled since 1975, 13% of adults are obese and 39% are overweight. In France, obesity impacts 17% of adults. This pathology also concerns more and more children and adolescents. In the under-18's 16% of boys and 18% of girls suffer from obesity.

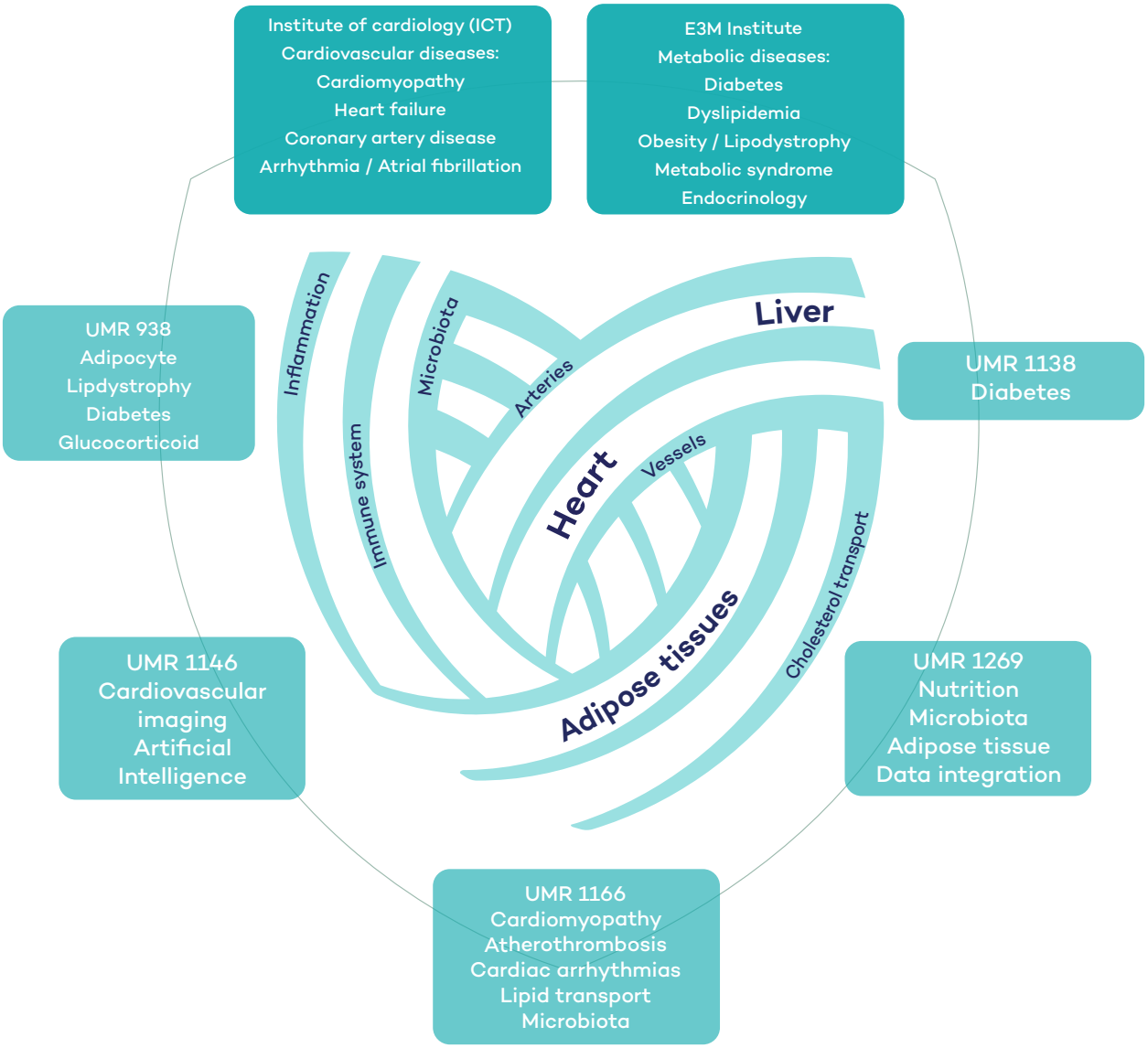
Liver diseases (Non-alcoholic steatohepatitis)

Also known as "fatty liver disease" or "soda disease", non-alcoholic steatohepatitis, or "NASH" is a chronic disease consisting in the accumulation of fat in the liver (steatosis), and is associated with metabolic risk factors (obesity, type 2 diabetes, etc.), and not related to an excessive consumption of alcohol. NASH is a disease that is constantly evolving around the world. The number of people suffering from metabolic steatosis is growing sharply, and will continue to rise in the years to come, the upsurge in cases of type 2 diabetes and obesity worldwide. It concerns 18% of the adult population in France (25% globally, 32% in the United States).

THE 4 PILLARS OF THE IHU ICAN

1/ A fundamental and clinical research community:

Since 2012, a community of scientific and medical experts work together under the aegis of IHU ICAN.



2/ Scientific platforms and cutting-edge research platforms

The scientific platforms

IHU ICAN BioCollection
Biobanking

IHU ICAN BioCell
Flow Cytometry

IHU ICAN BioCell
Human Liver Biology

IHU ICAN BioCell
iPS

IHU ICAN Omics
Lipidomics

IHU ICAN Omics
Metabolomics

IHU ICAN I/O
Data Sciences

The research platforms

IHU ICAN Clinical Investigation
Cardiometabolic Diseases

IHU ICAN Imaging
MRI & Core Lab

Learn more about the platforms on page 29

The collaborations

scai
SORBONNE CENTER FOR ARTIFICIAL INTELLIGENCE

SCAI groups together a strategic spectrum of contemporary artificial intelligence disciplines in the centre of Paris at Sorbonne University and also at Sorbonne University Abu Dhabi. Its objective is to make a significant contribution to excellence in research and interdisciplinary training in artificial intelligence, prioritising interactions between teachers, researchers, students and private sector partners. SCAI works in close collaboration with the teams at ICAN.

Find out more on page 74

metagenopolis mgps.eu

MetaGenoPolis (MGP) is an EPST (Public Scientific and Technical Research Establishment) unit specialising in the science of the gut microbiome applied to nutrition and health. MGP's expertise in the field of intestinal microbiome analysis and its role in health and diseases has been internationally recognised by the scientific community since 2010. MetaGenoPolis works in collaboration with the teams from the IHU ICAN, which is one of its founding members.

Find out more on page 75

3/ The clinical cohorts

- **More than 40,000 patients and healthy volunteers** included in clinical cohorts and trials
- **General population, primary prevention, metabolic diseases, rare diseases** and **transplants etc.**
- **Longitudinal data** with more than 10 years of follow-up for some registries

COHORTS

FH-CALC
(hypercholesterolemia)
270 patients

SUPAT - PCV
(Prévention CV)
25 000 patients

METACARDIS
800 patients
Europe Extension
> 2 000 malades

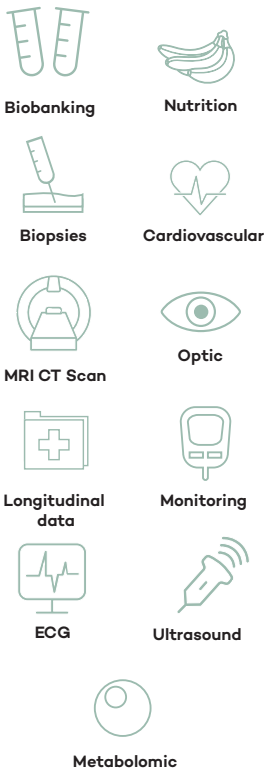
FRAMES
(metabolic steatosis)
500 patients
Europe Extension
EpOS / Litmus
> 8 000 patients

National Channel CARDIOGEN
2 660 patients CMH
3 210 patients CMD
1 000 patients ARVC
Europe Extension ERN

FASTRHAC
(FA)
300 patients

ATLANTIS
(TAVI)
1 500 patients

Transplantation Cohort
Heart and Liver
> 1 000 patients



4/ The flagship projects

- **28 Major collaborative projects** of which 2 transatlantic networks and 8 European initiatives
- **3 European projects** coordinated by IHU ICAN researchers (METACARDIS, MAESTRIA and CMRAI)

The IHU ICAN has developed cutting-edge expertise in setting up academic projects and supporting industrial projects, from the design and implementation of studies through to the validation of research, including regulatory funding aspects.

Future investments | Europe | AP-HP | North America | National

NON ALCOHOLIC STEATOHEPATITIS

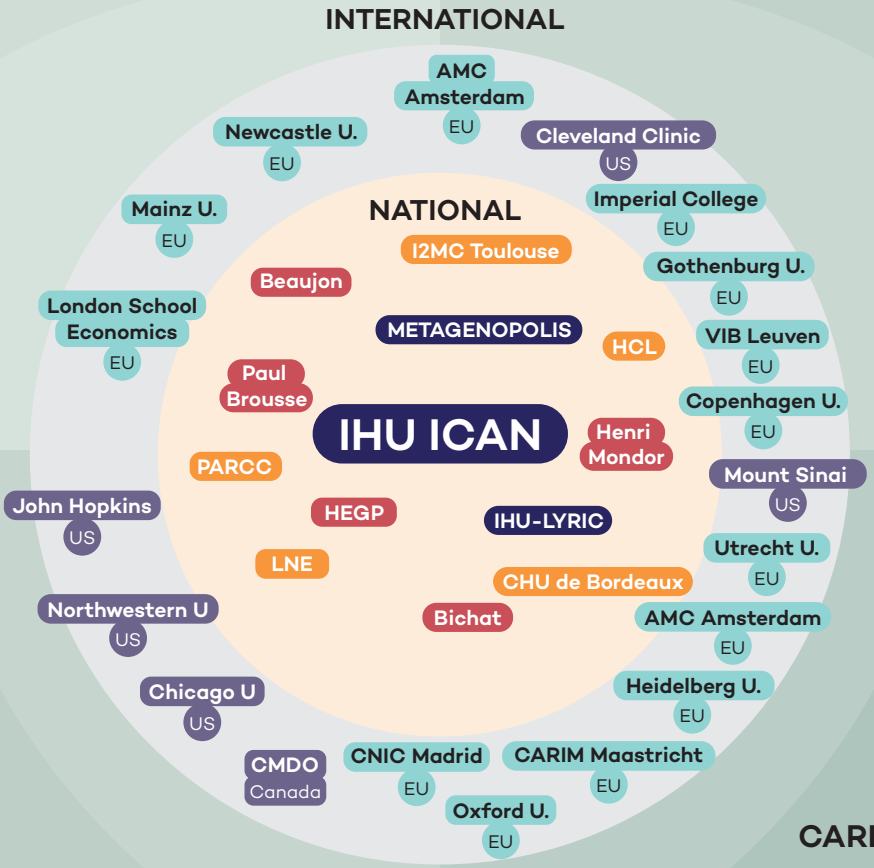
Major Collaborative projects

FP7 FLIP
IMI SAFE-T
H2020 EpOS
IMI2 LITMUS
ISR HOTSUFR
IMI2 EU-PEARL

NUTRITION

Major Collaborative projects

F-CRIN FORCE NETWORK
FP7 METACARDIS
Leducq Microbiome



CARDIOPATHIES

Major Collaborative projects

FP7 CULPRIT-SHOCK
FP7 BESTAGEING/MON4STRAT
Leducq Cardiac Regeneration
PSPC CALYPSO
RHU CARMMA
H2020 CATCH-ME
H2020 MAESTRIA
IMI COMBACTE-MAGNET
IMI2 CARDIATEAM
ERN GUARD-Heart
International Lab (Mt Sinai)
Horizon Europe HORUS

CARDIOMETABOLIC BIOMARKERS

Major Collaborative projects

PSPC PACIFIC
RHU CHOPIN
ISR FH CALC
International Lab (John Hopkins)
EIT CMR[AI]
EMPIR CARDIOMET
ISR ICARD

THE RESEARCH TEAMS

11 research teams with specialist expertise in cardiometabolism

Research unit 1166 for cardiovascular and metabolic diseases
Prof. Stéphane HATEM
Created in 2014, this joint research unit is wholly devoted to research into cardiovascular and metabolic diseases around four main AXIS: atherothrombosis and coronary diseases, the genomics of cardiomyopathies and heart failure, atrial fibrillation and cardiac arrhythmias, lipids and atherosclerotic vascular diseases.

- **Team 1** - Genomics and Physiopathology of Myocarditis Diseases
  Prof. Philippe CHARRON

- **Team 2 -** Atherothrombosis and Applied Pharmacology
  Prof. Jean-Philippe COLLET

- **Team 3** - Molecular and Cell Plasticity in Cardiovascular Diseases
  Sophie NAUDAD and **Elise BALSE**

- **Team 4** - Systemic and Cellular Lipidic Metabolism in Cardiometabolic Diseases
  Wilfried Le GOFF

- **Team 5** - Mononuclear phagocytes in cardiometabolic diseases
  Philippe LESNIK

UMR 1146 - Biomedical Imaging Laboratory (LIB) CNRS - INSERM
Team - Cardiovascular Imaging
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 IHU-ICAN

- **Team 9** - Lipodystrophies, metabolic and hormonal adaptations, and ageing
  Prof. Bruno FÈVE

- **Team 11** - Metabolic fibro-inflammatory and liver bile diseases led by
  Prof. Chantal HOUSSET

- **Team 12** - IFG system, foetal and post-natal growth
  Prof. Irène NETCHINE

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

UMR 1269: Nutrition and obesities: systemic approaches (nutriomics)
Prof. Karine CLÉMENT

THE CLINICAL TEAMS

The IHU ICAN brings together internationally renowned clinical experts.

ARCHIMEDE MEDICAL-UNIVERSITY DEPARTMENT (DMU)

Prof. Richard ISNARD

The ARCHIMEDES DMU brings together the clinical departments and units of the Sorbonne University Hospital Group involved in the care and treatment of acute and chronic cardiovascular and metabolic diseases, as well as certain rare pathologies. The DMU meets the objective of providing of coherence of care in these pathologies across eastern Paris, and improving the treatment plans with teams that have a long history of collaboration together, and a strong local, national and international visibility.

Pitié-Salpêtrière Hospital Group
Institute of Cardiology

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

E3M Institute

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

SAINT-ANTOINE HOSPITAL GROUP

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

Centre for Clinical Research (CCR) Paris-East
Prof. Christian FUNCK BRENTANO

Research Centre in Human Nutrition (CHNR)
Prof. Jean-Michel OPPERT

CARDIOVASCULAIRE AND THORACIC IMAGING DEPARTMENT CTI (DMU DIAMENT)

Prof. Alban REDHEUIL

CTI is the cardio-radiology department at Pitié Salpêtrière dedicated to cardiac, vascular and thoracic imaging. The team is involved in research within the framework of the MRI platform and the Core Lab imaging of the IHU ICAN, and several of its medical staff are long-standing members of the cardiovascular team at the LIB (biomedical imaging laboratory) (INSERM/CNRS).

Rhythmology team

GOVERNANCE

The IHU is led by a board of trustees

It sets overall policy. It is composed of 13 members: 3 founding members, 5 qualified persons, 3 representatives from the financial world and 2 representatives elected by the research teachers.

Composition
Thierry TUOT, President of the Board of Trustees - Counsellor of State

Founders representatives
Gilles BLOCH, President and chief executive of INSERM
Nathalie DRACH-TEMAM, President of Sorbonne University
Martin HIRSCH, Chief Executive of AP-HP (succeeded by Nicolas Revel in July 2022)

Permanent invitees
Elli CHATZOPOULOU, Director of partnerships and external relations, INSERM
Milan LAZAREVIC, AP-HP, clinical research and innovation directorate / acting deputy director
Bruno RIOU, Dean of the faculty of Medicine Sorbonne University

Qualified Persons
Catherine BOILEAU, MD, PhD AP-HP,
Claudine CANALE, President, The Poids Plumes Association
Ehrlich DUSKO STANISLAV, Director of Research INRA
Jessica LEYGUES, CEO, MEDICEN, Paris Region

Representatives from the private sector
Laurence COMTE-ARASSUS,
GE Healthcare, Chief Executive, FBFA zone, Representative for SNITEM
Pierre SONIGO, SEBIA, Director, R&D and medical commerce
Philip JANIAK, Chief Executive of Corteria Pharmaceuticals

Representatives for the researchers and teacher-researchers
Bruno FEVE, Head of Department and for the CRSA - JRU 938 Research Centre
Corinne FRERE, MCU-PH, Haematology, AP-HP

General Management and Executive Committee?

Prof. Stéphane Hatem has been IHU ICAN's chief executive since 2018. He was unanimously reappointed for a 4 years tenure by the board on the 16th of December 2021. The chief executive oversees the general management of the IHU and is seconded by a General Secretary, who is responsible for the operational management of the Institute. The IHU's management duo is supported by an executive committee composed of 6 members.

Prof. Stéphane Hatem, Chief Executive
Stéphane Barritault, General Secretary
Stéphane Commans, Manager of the Innovation and Research Valorisation unit
Ludovic Le Chat, Manager of the Business Development platforms unit
Jeanne Haidar, Manager of the Clinical Investigation Platform
Maud Decraene, Manager of the Legal, Compliance and Data Policy unit
Stéphanie Lapous, Manager of the Administration, HR and finance unit
Francine Trocmé, Manager of the Communication and Sponsorship unit

The Executive Committee (COMEX)

The COMEX is comprised of the chief executive, the general secretary, the heads of the IHU's internal divisions and one community representative per strategic axis. The Director of the Pitié-Salpêtrière Hospital Group and the Medical Director of the MUD are permanent invitees. COMEX is tasked with helping the chief executive, in particular in defining the IHU's strategy and scientific orientation, but also with all other aspects of management.

Prof. Fabrizio ANDREELLI, Endocrinology and Metabolism
Prof. Judith ARON-WISNEWSKY, Endocrinology and Metabolism
Prof. Eric BRUCKERT, Endocrinology, Metabolism and Prevention of Cardiovascular Diseases
Dr Olivier BOURRON, Diabetes (member in 2022)
Prof. Alain COMBES, Intensive Care Medicine
Dr Antonio GALLO, Prevention of cardiovascular diseases (member in 2022)
Prof. Estelle GANDJBAKHCH, Cardiology and vascular diseases
Prof. Richard ISNARD, Cardiology and vascular diseases
Mathilde LEFEVRE, Director of Research AP-HP Sorbonne University, succeeded in 2022 by **Loïc CARBADILLO**
Philippe LESNIK, Biology of atherosclerosis
Prof. Irène NETCHINE, Physiology - Paediatric Functional Investigation
Prof. Vlad RATZIU, Gastroenterology and hepatology
Prof. Alban REDHEUIL, Cardiovascular Imaging

IHU Board

The IHU Board is composed of the IHU 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 Archimedes MUD; and the department heads of this MUD involved in the ICAN's clinical activities.

The chair of the IHU board is the IHU's chief executive. Its objective is to strengthen internal cohesion of the IHU's medical and scientific community and to allow a flow of information between the teams to ensure overall consistency. The purpose of the IHU board is to enable an exchange and the sharing of the strategic orientations and scientific policy of the IHU.

Prof. Zahir AMOURA, Head of the Internal Medicine Department at the Pitié-Salpêtrière hospital
Elise BALSE, Head of the Molecular and Cellular Plasticity team within Cardiovascular Diseases – JRU 1166
Prof. Eric BRUCKERT, Head of the Endocrinology, Metabolism and Prevention of Cardiovascular Diseases Department
Prof. Philippe CHARRON, Head of the Genomic and Physiopathology of Myocardial Diseases research team, JRU 1166, and Director of the Reference Centre for Cardiomyopathies and Hereditary Cardiac Rhythm disorders
Prof. Laurent CHICHE, Head of the Cardiovascular Surgery Department at the Saint-Antoine hospital
Prof. Sophie CHRISTIN-MAITRE, Head of the Endocrinology, Diabetes and Reproductive Medicine department at the Saint-Antoine hospital
Prof. Karine CLEMENT, Head of the JRU 1269, Nutriomics - Nutrition and Obesities
Prof. Ariel COHEN, Head of the Cardiology Department of the Saint-Antoine hospital
Prof. Jean-Philippe COLLET, Head of the Interventional Cardiology Unit at the Institute of Cardiology Institute of the PSL HG, Head of Team 2, Atherothrombosis and Applied Pharmacology - JRU 1166
Prof. Alain COMBES, Head of the Intensive Care Department at the Pitié-Salpêtrière hospital
Prof. Bruno FEVE, Director of Research Unit 938 – Research Centre Saint-Antoine
Fabienne FOUFELLE, Head of the Metabolic Diseases, Diabetes and Comorbidities team - JRU 1138 Cordeliers Research Centre
Prof. Christian FUNCK-BRENTANO, Manager of the Centre for Clinical Research (CCR) Paris-East
Prof. Agnès HARTEMANN, Manager of the E3M Institute Diabetes Department
Prof. Chantal HOUSSET, Head of the Metabolic Fibro-inflammatory and Liver Bile Diseases team - Research Unit 938 - Saint-Antoine Research Centre

Prof. Richard ISNARD, Head of the ARCHIMEDES MUD
Nadjia KACHENOURA, Head of the Cardiovascular Imaging Team, JRU 1146
Wilfried LE GOFF, Head of the Systemic and Cellular Lipidic Metabolism in Cardiometabolic Diseases team - JRU 1166
Prof. Laurence LEENHARDT Head of the Functional Unit for Thyroid Pathologies and Endocrine Tumours
Prof. Pascal LEPRINCE, Head of the Cardiac Surgery Department at the Institute of Cardiology, Pitié-Salpêtrière Hospital Group
Philippe LESNIK, Head of the Mononuclear Phagocytes in Cardiometabolic Diseases team – JRU 1166
Prof. Gilles MONTALESCOT, Head of the Cardiology Department at the Institute of Cardiology, Pitié-Salpêtrière Hospital Group
Sophie NADAUD, Head of the Molecular and Cellular Plasticity team within Cardiovascular Diseases – JRU 1166
Prof. Irène NETCHINE, Head of the IFG System, Foetal and Postnatal Growth team, Research Unit 938 - Saint-Antoine Research Centre
Prof. Jean-Michel OPPERT, Head of the Nutrition Department at the E3M Institute and of the Research Centre in Human Nutrition (RCHN)
Prof. Christine POITOU BERNERT, Nutrition - Reference Centre Rare Genetic Obesities
Prof. Alban REDHEUIL, Head of the Cardiovascular Imaging Unit at the Cardiology Institute of the Pitié-Salpêtrière Hospital Group
Bruno RIOU, Dean of the faculty of Medicine
Prof. P. TOURAINE, Head of the Endocrinology and Reproductive Medicine department
Prof. Corinne VIGOUROUX, Reference Centre for Rare Insulin-Secretion and Insulin-Sensitive Pathologies (RISISP)

The Scientific Advisory Board

The scientific council was renewed in December 2021, to be enriched with people from the sciences recognised in the IHU ICAN's research fields, thereby providing an expert, critical and constructive view of the ICAN's scientific strategy. It is composed of 6 external members, highly recognised within the international scientific community in the fields of cardiometabolism and nutrition. This scientific governance body, designated by the Board of Trustees, is consulted on the IHU'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.

Prof. André CARPENTIER, Director of the "Diabetes, obesity and cardiovascular complications" axis of research, Faculty of Medicine and Health Sciences at the University of Sherbrooke, Canada
Prof. Arnold VON ECKARDSTEIN, Clinical Biochemistry, Laboratory Medicine and Pathology, University Centre for Laboratory and Pathology Medicine (UZL), Switzerland
Prof. Arnold Lesley HOYLES, Professor of Microbiome and Systems Biology Nottingham Trent University United Kingdom
Prof. Michaël RODEN, Professor of Endocrinology and Metabolic Diseases, University Hospital of Düsseldorf, Germany
Prof. Karin SIPIDO, Professor of Medicine and manager of Experimental Cardiology, University of Louvain, Belgium
Prof. Rozemarijn VLIEGENTHART, Radiologist and professor of Cardiothoracic Imaging, University Medical Center Groningen, Netherlands

Key Facts

MAESTRIA KICK OFF

MAESTRIA (Machine Learning and Artificial Intelligence for Early Detection of Stroke and Atrial Fibrillation), is an innovative research project that brings together 18 partners from Europe, the United States and Canada, selected under the H2020 Research and Innovation Actions call for proposals on digital diagnosis. The project launch was held in Paris, in the presence of all the partners, on the 27th and 28th of September 2021.

Coordinated by Prof. Stéphane Hatem, director of the IHU ICAN and the Inserm research unit JRU_S1166 at Sorbonne University, the MAESTRIA project aims to develop and validate the first digital platform for integrative diagnosis of atrial cardiomyopathy. By combining multimodal imaging data with patients' physiological data (omics, clinical, etc.), this platform will be able to identify new treatment targets for improved diagnostic accuracy. It will increase the efficacy and efficiency of treatment by better preventing the complications of atrial cardiomyopathy, such as atrial fibrillation and cerebrovascular accidents, two significant health problems.

This project is structured around three strategic AXIS:

- Personalised diagnosis and innovative, pluridisciplinary treatment plans
- Risk stratification in patients with Atrial Fibrillation
- Deployment of a pan-European digital diagnosis platform.

Find out more on page 54

NEW SCIENTIFIC ADVISORY BOARD

In 2021, the ICAN gained a new and equally prestigious Scientific Advisory Board (SAB). Six internationally-renowned scientists involved in cardiometabolic research now make up the new SAB. The SAB participates in defining the ICAN's scientific strategy and evaluates its scientific performance.

Prof. André CARPENTIER,
University of Sherbrooke
— Canada —
(new member)

Prof. Arnold VON ECKARDSTEIN,
University Centre for Laboratory and Pathology Medicine – UZL
—
Switzerland —

Prof. Lesley HOYLES,
Nottingham Trent University
— United Kingdom —
(new member)

Prof. Michaël RODEN,
Heinrich Heine University of Düsseldorf
— Germany —

Prof. Karin SIPIDO,
University of Louvain
— Belgium —
(new member)

Prof. Rozemarijn VLIEGENTHART, **University Medical Center of Groningen**
— Netherlands —

MEMBERSHIP OF THE FRENCH HEALTHCARE ASSOCIATION

In December 2021 the IHU ICAN became a member of the French Healthcare Association. This will boost development of its international influence and strengthen the construction of academic and manufacturing collaborations abroad.

French Healthcare

This association aims to federate all the players in the French healthcare ecosystem under a single banner in order to promote their know-how, technologies and innovations on an international scale. It is within this context that the IHU's management presented the IHU ICAN model at a series of conferences organised in January 2022 as part of the Research and Innovation in Healthcare fortnight at Expo Dubai.

THE BOARD OF TRUSTEES UNANIMOUSLY REAPPOINTED PROF. STÉPHANE HATEM AS CHIEF EXECUTIVE OF THE IHU ICAN

On the 16th of December 2021 the Board of Trustees unanimously reappointed Prof. Stéphane Hatem as the IHU ICAN's Chief Executive, with a new four-year mandate.

Prof. Stéphane Hatem, PU-PH and director of the Inserm JRU_S1166 cardiovascular and metabolic diseases research unit, had led the IHU ICAN since 2018.
During his first 4-year term, Stéphane Hatem reconstructed a management team and developed a new scientific project, to reposition the IHU ICAN as the leading player in cardiometabolism not only to undertake academic research but also large industrial projects. Ambitious research programmes have been launched in partnership with industrial (EIT Health, H2020), and the ICAN has initiated very promising collaborations with private partners (CorWave, Siemens, Imageens,etc.).
Now, with his new 4-year mandate, Stéphane Hatem's ambition is to develop the ICAN's international influence and to accelerate academic and manufacturing partnerships in order to develop a new approach to cardiometabolic diseases and in response to this major public health issue.

Cardiometabolic diseases are on the rise globally. The IHU ICAN teams are developing pluridisciplinary and innovative local and international projects to better understand the interactions between organs and tissues, and thus, to better manage the metabolic mechanisms that influence the onset and progression of cardiometabolic diseases."

Stéphane Hatem

NEW BRAND IDENTITY FOR THE IHU ICAN

The IHU ICAN took a big leap in terms of communication in 2021 by evolving its brand identity: new logo, new graphic charter, new identity, new website. After several months of collaborative work, the new visual identity of the IHU was born.

Interdisciplinarity
Interconnection
Data flows / Data

Loop / logo: Excellence
Statutory and reassuring

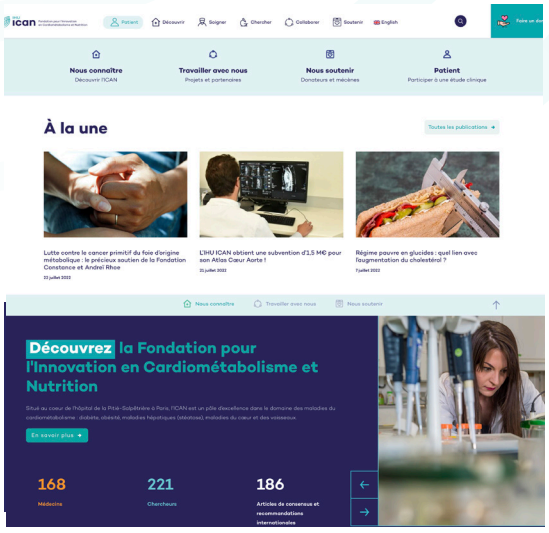
Cardiometabolism

IHU ican
Foundation for Innovation in Cardiometabolism and Nutrition

The new graphic identity reflects the central role played by the ICAN teams in prioritising collaborations and interactions between academic and private research, and between disciplines, to accelerate the development of a comprehensive, personalised approach to cardiometabolic diseases.
The new logo is the centrepiece of the IHU ICAN's new brand platform.

This new identity provides more space both for the IHU label and the ICAN's Foundation status. Indeed, the IHU label is positioned to be immediately visible, as proof of the excellence of the research projects carried out by the team. The customary name serves as a reminder of the areas of intervention - cardiometabolism and nutrition - as with the previous version, but it expresses 2 additional important and identifying elements: foundation and innovation.
The logo, in the shape of a loop, symbolises the desire to protect both the healthy and the sick thanks the innovative programmes, from foundational research through to clinical research.

Our new website www.ihuican.org is the culmination of the restructuring of our communications toolbox. It highlights the IHU's strengths, expresses the richness of actions taken by its experts and enables potential partners to quickly discover the scope of what the IHU services offer. The new website also makes it easy to support the ICAN via an integrated donation form. It is divided into 5 very clear navigation menus that allow visitors to easily find the information they are looking for: Discover, Care, Research, Collaborate, Support.
These navigation menus are complemented by a page dedicated to patients, which provides information on current research projects. Patients can thus find the information they need relating to the studies they are participating in.



2021 INITIATION OF THE SPONSORSHIP POLICY

Cardiometabolic diseases represent a public health challenge both in France and worldwide. In 2011, with the creation of the IHU ICAN, public authorities enabled the emergence of a new tool with which to manage those diseases: diabetes, obesity, NASH, heart and circulatory diseases, imprinting disorders.

A centre of excellence like the IHU ICAN makes it possible to concentrate medical and scientific expertise in order to undertake large-scale projects aimed at better understanding the interactions between organs and the genesis as well as the progression of metabolic and the ambition of developing, and has the ambition of developing precision medicine in cardiometabolism.

To fulfill its missions, the ICAN forges academic and industrial partnerships, collaborates with the best teams and has embarked upon a policy of sponsorship to accelerate, support and often make possible the innovative projects carried out by its teams. The support of sponsors is essential in conducting projects and piloting studies to reach proof of concept, and saves researchers the time needed for research funding applications.

The ICAN foundation, corporate partners and participating sponsors are working together to develop comprehensive and tailor-made care and treatment for cardiometabolic diseases. With the support of donors and sponsors, the ICAN foundation can fulfill its role as a discoveries accelerator, and converting those discovery into concrete actions for the benefit of patients.

The teams are grateful to the sponsors who support them in this wonderful adventure in the service of science and patients. Their commitment from the very beginning is a great sign of confidence.

BIOTRONIK, BOSTON SCIENTIFIC, CRÉDIT AGRICOLE ILE DE FRANCE MÉCÉNAT, ENTREPRENEURS AND GO, FEDERATION FRANCAISE DE CARDIOLOGIE, LA LIGUE CONTRE LA CARDIOMYOPATHIE, MEDTRONIC, MICROPORT

In 2021, the first year of the launch of its sponsorship policy, the IHU raised 225,000 Euros. That money has been allocated to innovative research projects.

Donations serve to develop ambitious programmes within the priority AXIS:

- **Imaging** to identify new metabolic diseases biomarkers, to improve the prevention, diagnosis and monitoring of treatment efficacity
- **Data, IA and cohorts** to create robust, collaborative and innovative research programmes that comply with regulations.
- **Biology of cardiometabolic diseases**, new interfaces: heart, microbiome, fatty tissue, cholesterol, liver to understand the mechanisms of the development and progression of cardiometabolic diseases
- **Rare diseases:** imprinting disorders.

To learn more about the IHU ICAN's sponsorship policy: www.ihuican.org

The research and clinical investigation platforms

ICAN CLINICAL INVESTIGATION

Presentation of the platform

Located in the E3M Institute at the heart of the Pitié-Salpêtrière Hospital site, ICAN Clinical Investigation is a clinical investigation platform dedicated to biomedical research. As experts in cardiometabolic diseases, the ICAN Clinical Investigation teams assist academic or industry developers in setting up their clinical projects and contribute to the smooth running of clinical trials, from the feasibility stage and the selection of a centre through to project completion. Thanks to its unique location within the largest public hospital in Europe, ICAN Clinical Investigation is the ideal interlocutor to coordinate the different clinical wards located within Pitié-Salpêtrière and the the APHP Clinical Research and Innovation Department (DRCI) to implement innovative academic and industry sponsored clinical research projects.

Collaborations

The clinical investigation platform collaborates with several clinical teams at the Pitié Salpêtrière and Saint-Antoine hospitals. The clinical investigators from the intensive care, cardiology, endocrinology, hepatology, nutrition and cardiothoracic imaging departments trust it to manage and properly execute their studies. Studies can be conducted on both common and rare pathologies.

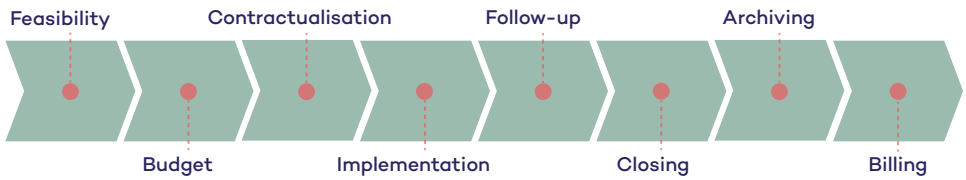
EN 2021 THE PLATFORM COLLABORATED IN 53 STUDIES, INCLUDING:

FH-CALC Study

Coronary calcification study in subjects with heterozygous autosomal dominant familial hypercholesterolemia.

Familial hypercholesterolemia (FH) is a autosomal dominant genetic disease characterised by elevated plasma concentrations of LDL cholesterol.

ICAN CLINICAL INVESTIGATION CHAIN OF INVOLVEMENT



Familial hypercholesterolemia is triggered by at least three distinct genetic conditions caused by gene mutations: (1) of the LDL particle receptor, (2) of apolipoprotein B and (3) of the pro-protein convertase subtilisine / kexine 9. The clinical phenotype that results from these mutations is variable and exists in “heterozygotic” forms (heFH) and “homozygotic” forms (hoFH).

This project is part of the wider context of premature ageing of the cardiovascular system, with consequences for the development of cardiovascular complications such as vascular calcification.

The study population is asymptomatic patients with genetically determined heterozygous familial hypercholesterolaemia.
The FH-CALC clinical research project was designed to identify infraclinical alterations of the vascular tree, in order to improve treatment of heHF and to prevent the disease’s long-term complications.

The main objective is to assess the prevalence of elevated coronary calcium (> 75th percentile according to the MESA reference population) in a population of asymptomatic patients with familial hypercholesterolemia using cardiac tomodensitometry to identify new markers of myocardial and arterial dysfunction and thus be able to suggest adapted prevention.

This is nation-wide clinical investigation, with 2 Parisian AP-HP centres: the Pitié-Salpêtrière and Saint-Antoine hospitals.

Between June 2018 and June 2021 260 patients were included at the Salpêtrière site, out of a total of 300. The study was conducted over a 3-year period and there has been no need to extend the timeframe to achieve its objectives, despite Covid lock-downs.

The project will contribute to improved knowledge of hypercholesterolemia and its impacts.

SAFIR Study

Study of the phenotypeS of pAtients from Families with genetIc hypercholesteRolemia - SAFIR; Genetic Study in routine care, Multi-centre case-control.

Atheromatous cardiovascular diseases (myocardial infarction), cerebral vascular accidents (CVA), and peripheral arterial disease (PAD) are a major cause of morbidity and mortality in Europe. Among the cardiovascular risk factors, increased cholesterol linked to low density lipoprotein (LDLC) plays a central role in the development and progression of atherosclerosis. In numerous randomised studies statins, which lower concentrations of LDL cholesterol, have been shown to have a beneficial effect on lowering cardiovascular risks.

The extent of biological disruption resulting from heterozygous familial hypercholesterolemia (FH) (significant, prolonged “lifelong” elevation of LDL-C) expose patients to an extremely high risk of early atherosclerosis. However, significant clinical and imaging heterogeneity in vascular complications in HF patients has been observed . This heterogeneity cannot be explained simply by the presence of other cardiovascular risk factors (smoking, arterial hypertension, diabetes) or by differences in efficacity and/or observance of treatment.

Based on this observation, the SAFIR study aims to identify new genetic markers responsible for cardiovascular protection in patients with familial hypercholesterolemia (FH).

The primary goal of the SAFIR study is thus to identify atheroprotective genetic factors in these patients, which will in turn enable the identification of new treatment targets for the treatment of CV diseases and FH. Additionally, SAFIR aims to enable the identification of new CV protection biomarkers, which will be useful tools for developing personalised medicine for the treatment and care of dyslipidemia.
It is a multi-centre national study involving 8 centres: (Nantes, Paris Pitié Salpêtrière and St Antoine, Marseille, Dijon, Lyon, Rennes,Toulouse, Lille). The constitution

of the cohort was done at the leading lipidology reference centres, contributing to the creation of a French register of FH under the aegis of the New Francophone Society for Atherosclerosis (Nouvelle Société Francophone d'Athérosclérose; NSFA). The goal was to recruit at least 200 compelling subjects and relatives with FH free of any cardiovascular complications and with a low coronary calcic score, while in parallel to recruit at least 400 compelling subjects and relatives with FH with high cardiovascular risk, in order to identify interesting genetic markers in the so-called "free" population. Furthermore, in order to be able to discriminate between genes of interest and/or pathogens for familial hypercholesterolemia, the study needed to recruit relative of these families who were not suffering from familial hypercholesterolemia (1 to 2 per family), i.e. 600 patients in total.
Between March 2018 and May 2021, the IHU ICAN included 149 patients, of which 62 were FH-free, and ranked first nationally in terms of recruitment for the SAIFIR project.

The SAFIR study is part of a larger research programme called CHOPIN (CHOlesterol Personalized Innovation), which offers the advantage of bringing together complementary expertise for genetic, lipidomic and metabolomic analyses from a consortium of 15 partners,. This consortium also brings together numerous clinicians from within the reference centres, for FH patient phenotyping. CHOPIN seeks to develop personalised medicine for hypercholesterolemia, by identifying new CV risk markers and new LDL-C metabolism targets in high-risk subjects due to increased LDL-C.
The originality of the SAFIR project is the clinical observation starting point: unexpectedly, many families of patients with familial hypercholesterolemia do not develop cardiovascular complications.

53
active studies of which 14 new studies that started in 2021
28 academic, and **27** drug or medical device industry sponsored

14
new studies

350
new patients included in the studies and more than **1,000** patients included in the cohorts each year.

The team
Manager:
Jeanne HAIDAR

- Deputy manager: **Choukri TRIQUI**
- Clinical Research Practioners:
  Dr Emmanuelle Bégot / Dr Raluca PAIS
- Clinical Research Nurses:
  Aurélie FONTANIER / Thomas MAUREL
- 10 clinical research technicians: **Selma ABID, Carole BERNHARDT, Anissa BOUABDALLAH, Stéphanie COMBET, Hanane GUERMOUDI, Hayet IDDIR, Valentine LEMOINE, Madjid OUDIHAT, Sophie SAUN, Maryse SEDJI**

THE IMAGING PLATFORM: ICAN IMAGING

NEW IMAGING TECHNIQUES SUCH AS MRI NOW ENABLE EARLY DIAGNOSES OF DISEASES, BY DETECTING STRUCTURAL ANOMALIES OR ORGAN FUNCTION AT AN INFRA-CLINICAL POINT."

Prof. Alban Redheuil

Presentation

The IHU ICAN's purchase of a next-generation 1.5T cardiovascular MRI enabled the creation of the first cardiovascular and metabolic magnetic resonance imaging platform entirely dedicated to interventional human research in Île-de-France. This platform enables academic and industry lead research projects to be conducted, by offering advanced quantitative non-invasive imaging of the cardiocirculatory system, and the development of metabolic imaging:

- Acquisition of standardised and optimised images
- Clinical research protocols
- Methodological and technological protocols
- Access to imaging from the cohort and population
- Quality control and data management / GDPR -compliant archiving

Core Lab

The centralised laboratory for image analysis, created in 2014, offers bi-modal analysis (CT scan and MRI). The principal activities encompass:

- Medical reading, expert labelling, adjudication
- Internationally-recognised expertise in processing cardiovascular images
- An offering of tailor-made analysis in the context of diagnostic/therapeutic studies

Collaborations

The platform works jointly with the "cardiovascular imaging" team of the LIB (Nadjia Kachenoura, DR Inserm) and the medical and paramedical team at the cardiothoracic imaging unit (ICT) at Pitié-Salpêtrière (Prof. Alban Redheuil).

In 2021, Corelab was the centralisedimaging review and post-processing centre for the industry-promoted Quorum study, which aims to use imaging biomarkers to demonstrate the efficacy of a new drug in treating myocardial infarction. 1,100 examinations were reviewed, certified and analysed in this way.

1,100

EXAMINATIONS ANALYSES (MRI AND CT SCAN)

5 publications

We also finalised the analysis of cardiac MRIs within the context of the Corticoeur PHRC (a clinical research hospital program), in collaboration with the endocrinology department at Bicêtre hospital, for which the main objective is to quantify myocardial steatosis in patients with hypercortisolemia, before and after treatment. The completion and start of the first acquisitions took place during 2021 using innovative sequences obtained thanks to a partnership with Siemens Healthineers.

The team
MRI and CoreLab manager: Khaoula Bouazizi, PhD

- Scientific managers: **Prof. Alban Redheuil (AP-HP)** and **N. Kachenoura (Dr INSERM)**
- Research engineer: **Ali Kilinc**
- Research Engineer: **Mohamed Zarai**
- Radiographer: **Mikaël Prigent**.

2021 PUBLICATIONS

1. Epicardial and Pericardial Adiposity Without Myocardial Steatosis in Cushing Syndrome. Wolf P, Marty B, Bouazizi K, Kachenoura N, Piedvache C, Blanchard A, Salenave S, Prigent M, Jublanc C, Ajzenberg C, Droumaguet C, Young J, Lecoq AL, Kuhn E, Agostini H, Trabado S, Carlier PG, Fève B, Redheuil A, Chanson P, Kamenický P. J Clin Endocrinol Metab. 2021 Nov 19;106(12):3505-3514.

2. Abdominal adipose tissue components quantification in MRI as a relevant biomarker of metabolic profile. Bouazizi K, Zarai M, Dietenbeck T, Aron-Wisnewsky J, Clément K, Redheuil A, Kachenoura N. Magn Reson Imaging. 2021 Jul;80:14-20.

3. Cardiac adipose tissue volume and IL-6 level at admission are complementary predictors of severity and short-term mortality in COVID-19 diabetic patients. Cardiovasc Diabetol. Phan F, Boussouar S, Lucidarme O, Zarai M, Salem JE, Kachenoura N, Bouazizi K, Charpentier E, Niati Y, Bekkaoui H, Amoura Z, Mathian A, Benveniste O, Cacoub P, Allenbach Y, Saadoun D, Lacorte JM, Fourati S, Laroche S, Hartemann A, Bourron O, Andreelli F, Redheuil A; COVID-19 APHP.SU Group. 2021 Aug 12;20(1):165.

4. Adipose tissue fibrosis assessed by high resolution ex vivo MRI as a hallmark of tissue alteration in morbid obesity. Bouazizi K, Zarai M, Marquet F, Aron-Wisnewsky J, Clément K, Redheuil A, Kachenoura N. Quant Imaging Med Surg. 2021 May; 11(5):2162-2168.

ICAN BIOBANKING & BIOCOLLECTION

Presentation

ICAN's Biobank (CRB) BioCollection integrates activities of sample handling, sample processing (centrifugation, aliquoting, DNA and RNA extraction, etc.), storage at -20°C, -80°C and -150°C with temperature monitoring and provision of biological resources. Several types of biological samples are thus preserved within ICAN BioCollection: serum, plasma, buffy coat, adipose tissues (sub-cutaneous, mesenteric, omental), hepatic tissues, urines, stools, salivas etc. New sample processing can also be implemented on request by the user.

EURO-QUALITY SYSTEM ISO 9001:2015

EURO-QUALITY SYSTEM NF S96-900

Our BRC is ISO 9001 certified: 2015; and NF S 96-900: 2011 since December 2019.

Collaborations

ICAN BioCollection works in close collaboration with the clinical investigation platform and participates in around twenty academic and industry sponsored clinical studies across all areas of cardiometabolism, from nutrition to cardiac surgery, via endocrinology and hepatology.

In 2021

The acquisition of two freezers (storage and backup) created new storage capacity at -150°C.

12
active collections

187
DNA EXTRACTIONS

22
care and treatmen protocols

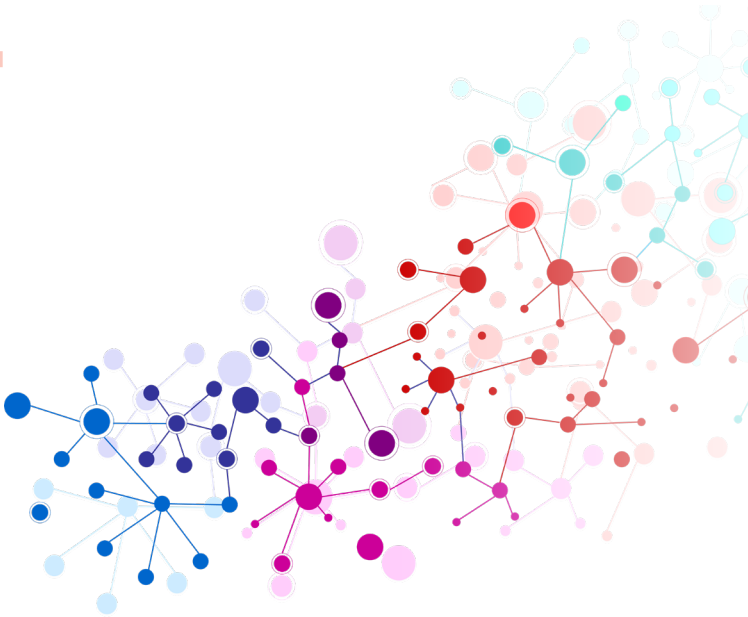
6 ,108
samples collected and **7,901** samples made available

The team

Manager:
Sara Cipriani, PhD

- 3 laboratory technicians: **Jean-Baptiste Blond**, **Ludivine Harmand**, **Houdah Ali Kassim**.

ICAN I/O – NEW PLATFORM



Presentation

ICAN I/O is a platform with expertise in analysis and integration of multi-omics and clinical data. Created in 2011, the platform relies on recent technological evolutions, with an increasing use of robust algorithms that meet research objectives through a collaborative and holistic approach integrating multi-omics technologies and statistical analysis.
The purpose of the platform is to address all subjects related to biomedical research data (Data governance, data management, data science).

Collaborations

We created this platform in 2021, giving it an outline and an expanded role that brings together all data-related functions. Our platform is already engaged in significant projects, such as MAESTRIA, and has been involved in hepatology and cardiology studies.

The team

Manager:
Maharajah Ponnaiah. PhD

- 2 data managers: **Mehdi Menai** and **Romain Chenu.**
- 1 health and artificial intelligence data projects: **Waed Khalek**

2021 Publications

1. Extracorporeal membrane oxygenation network organization and clinical outcomes during the COVID-19 pandemic in Greater Paris, France: a multicentre cohort study. Lebreton et al. The Lancet, 2021

In this multi-centre cohort study, an analysis is presented of all adult patients with laboratory-confirmed SARS-CoV-2 infection and severe ARDS requiring ECMO who were admitted to 17 intensive care units in the Greater Paris area between March 8 and June 3, 2020. The survival of COVID-19 patients given ECMO for 90 days was strongly associated with a center's experience with vein-venous ECMO during the previous year. ICAN I/O undertook statistical analysis and validated the models using machine learning algorithms.

2. Predicting 90-day survival of patients with COVID-19: Survival of severely ill COVID (SOSIC) scores. Schmidt et al. Ann Intensive Care, 2021

The goal of this study was to develop predictive survival models for patients with COVID-19 after 1 to 2 weeks in intensive care. Based on the COVID-ICU cohort, which undertook a prospective collection of the characteristics, management and results of patients who were severely ill with COVID-19. Machine learning was used to develop dynamic, clinically useful models capable of predicting mortality to 90 days using ICU data collected on day (D) 1, D7 or D14. This enabled the development of a score, the SOSIC, which is accessible via an online calculator: https://sosic.shinyapps.io/shiny.

ICAN OMICS

IBiSA Infrastructures en Biologie Santé et Agronomie

ICAN OMICS Lipidomics and Metabolomics have been IbiSA certified since 2020

1/ LIPIDOMICS

Presentation

In close liaison with the ICAN community's researchers and clinicians, the lipidomics platform, whose scientific manager is Anatol Kontush, is particularly committed to identifying new lipid biomarkers in the area of cardiometabolism and nutrition, with the aim of improving prevention and refining the stratification of patients for a more personalised treatment. Our platform offers complex profiling (quantification of more than 500 lipid species) and targeted approaches for the study of specific metabolic pathways (sphingolipid metabolism, energy metabolism, cholesterol metabolism, metabolism of intestinal microbiota).

Collaborations

With around fifteen projects underway, our lipidomic platform is working for several teams from the ICAN community at the Pitié Salpêtrière hospital group site, and also with other academic teams in France and abroad.

In 2021 we finalised development of a targeted and quantitative assay for sphingosines, sphingosine-phosphate and bile acids. We started the development of an acylceramide assay.

145 species added to the catalogue

4 publications

3,157 SAMPLES ASSAYED

2021 PUBLICATIONS

1. Impacts of a high fat diet on the metabolic profile and the phenotype of atrial myocardium in mice. Suffee N et al. Cardiovasc Res. 2021,

2. Phospholipid transfer to high-density lipoprotein (HDL) upon triglyceride lipolysis is directly correlated with HDL-cholesterol levels and is not associated

ICAN OMICS

2/ METABOLOMICS

Presentation

The strategy developed within our platform, for which the scientific manager is Philippe Lesnik, is based on the profiling of a large number of metabolites using multi-disciplinary expertise combining bio-tech tools, statistics and biochemical databases to interpret the results with the help of a high resolution mass spectrometer coupled with chromatographic systems. Our platform offers targeted approaches for the study of potential markers or specific biochemical pathways, as well as a non-targeted approach enabling research in new biomarkers.

Collaborations

With around fifteen projects underway, our metabolimic platform is working for several teams from the ICAN community at the Pitié Salpêtrière hospital group site, and also with other academic teams in France and abroad.
Our platform also has several partnerships and services with the industry.

In 2021

We contributed to the implementation of bile acid assays via the lipidomic platform. Several development projects were initiated to enhance our approaches, with the development of annotation tools for the overall approach, and the implementation of a pre-analytical approach using automated sample pre-treatment. The streamlining of these stages will allow the entire Omics platform to optimise its pipeline to meet the challenges of clinical cohort analyses and European projects (H2020 MAESTRIA, H2020 GoDS1) in which the platform is involved.

2,941 samples assayed

3 publications

Development of an annotation tool using a public database that lists more than **43,000 chemical entities**

The team

- **ICAN Omics Lipidomics manager: Marie Lhomme PhD**
- **ICAN Omics Metabolomics manager: Farid Ichou, PhD**

◦ Laboratory technician: **Sora Lecocq**

with cardiovascular risk. Ma F et al, Atherosclerosis. 2021.
3. Transgenerational supplementation with eicosapentaenoic acid reduced the metabolic consequences on the whole body and skeletal muscle in mice receiving an obesogenic diet. ***Pinel A et al., Eur J Nutr. 2021,***

4. Endothelial Lipase Modulates Paraoxonase 1 Content and Arylesterase Activity of HDL. Schilcher I et al., Int J Mol Sci. 2021

ICAN BIOCELL

BIOCELL-IPS

Presentation

The possibility of developing pluripotent stem cells (inducible pluripotent stem cells, iPSc) from adult cells, in other words cells capable of differentiating into other adult cell types, has revolutionised the study of the molecular mechanisms of human diseases. The ICAN BioCell iPS platform, for which the scientific manager is Eric Villard, specialises in the production and genetic modification of iPS cells, and in their differentiation into highly specialised cells such as cardiomyocytes, endothelial cells, adipocytes, hepatocytes and intestinal cells.

Collaborations

Our platform principally works on two AXIS; cardiomyopathies with a genetic origin, and metabolic diseases with parental imprinting. The studies on these pathologies require the differentiation of iPS into numerous cell types (cartilage and growth chrondocytes, hepatocytes, cardiomyocytes).

In 2021

The platform was involved in 6 parallel research projects, of which two were European projects (Scale EraNet and Rediscard). We have finalised the differentiation of the iPS into endothelial cells, and a reprogramming method to retain of the methylation status of a patient's cells within the iPS produced. An additional axis involving the production of organoids was initiated and is in development. Several types of organoids have been developed.

4
genomic editions

150
clones iPS produced from Silver-Russel and control patients.

40 CLONES OF CARDIOMYOCYTES PRODUCED

2
PUBLICATIONS

The team

Manager:
Vincent Fontaine, PhD

- 2 assistant engineers:
  Sibylle Marteau and Céline de Flori.

2021 PUBLICATIONS

Generation of iPSC line from MYH7 R403L mutation carrier with severe hypertrophic cardiomyopathy and isogenic CRISPR/Cas9 corrected control. Genome-wide association analysis in dilated cardiomyopathy reveals two new players in systolic heart failure on chromosomes 3p25.1 and 22q11.23. Garnier et al. Eur Heart J. 2021 May 21;42(20):2000-2011. Fontaine et al. Stem Cell Res 2021 Apr;52:102245

ICAN BIOCELL

BIOCELL-HUMAN LIVER BIOLOGY

Presentation

The ICAN BioCell Human Liver Biology platform, for which the scientific managers are Chantal Housset and Filomena Conti, aims to produce primary human hepatic cells (hepatocytes and all the non-parenchymatous cells) and to develop primary culture hepatic models, in 2D or 3D (Precision cut or spheroid slices) to study chronic liver diseases, in particular fibrosis and NASH.
Our platform also has a collection of characterised hepatic myofibroblasts from different patients (normal and cirrhotic).

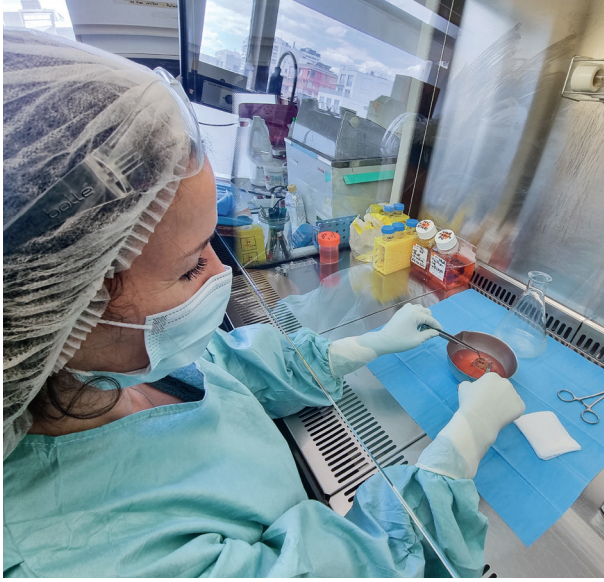
Collaborations

Our platform benefits from a well-established collaboration with the digestive surgery, hepato-bile-pancreatic and liver transplant department at the Pitié-Salpêtrière hospital group, which gives us access to normal and cirrhotic livers.
We collaborate both with ICAN's academic community and industry partners.

In 2021

We finalised the development of hepatic spheroids, which allows us to offer a functional 3D hepatic model for 12 days, to study NASH and hepatic fibrosis.

The platform has also obtained a **CODECOH, DC-2020-3900** and **AC2020-3861** for
- The preparation of human cells for the purpose of scientific research and collaboration.
- Authorisation to store, process and transfer human cells



2 publications

21 SAMPLES RECEIVED AND USED

The team

Manager:
Lynda Aoudjehane, PhD

- 1 assistant engineer: **Camille Zaniolo.**

PUBLICATIONS 2021

1. Ex-Vivo Pharmacological Defatting of the Liver. Goumard C, Turco C, Sakka M, Aoudjehane L, et al. J Clin Med. 2021 Mar 18;10(6):1253

2- Modulatory effect of rapamycin and tacrolimus on monocyte-derived dendritic cells phenotype and function. Dahlqvist G, Renaud S, Barjon C, Lefebvre A, Aoudjehane L et al. mmunobiology. 2021 Jan ;226(1):152031. doi:10.1016/j.imbio.2020.

ICAN BIOCELL

BIOCELL-FLOW CYTOMETRY

Presentation

The BioCell-Flow Cytometry platform offers a range of services based on multiparametric flow cytometry, cell sorting and the characterisation of cytokines and chemokines by Bioplex analysis. The platform has scientific and technical capabilities for a large range of scientific projects in life sciences. Thanks to is scientific and technical expertise, the ICAN BioCell-Flow Cytometry platform staff can assist over the duration of your project, from conception through to analysis and preparing the results for publication.

Collaborations

Our platform works for around twenty teams from within the ICAN community at the Pitié-Salpêtrière hospital group and the Sorbonne University, and with industry partners.

Within the Joint Laboratory, together with Hybrigenics Services, OptiMAb, the platform contributed to the validation of an antibody against Lipocalin, a transport protein for hydrophobic molecules (lipids, steroids).

574 HOURS OF ANALYSIS AND SORTING

32 **hours of training**

30 **advisory hours**

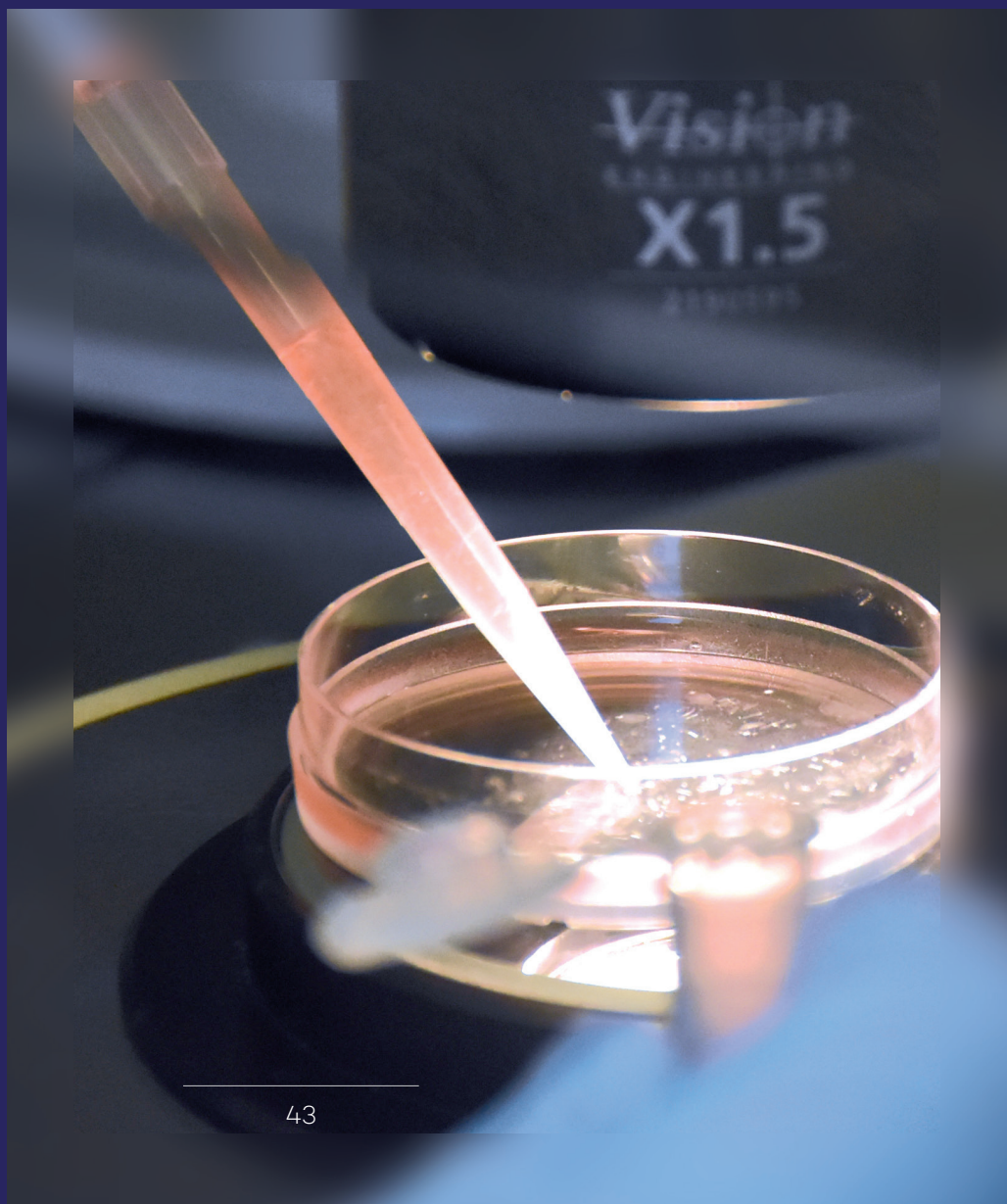
The team

Sara Cipriani, PhD

- 1 study engineer: **Aurélie Gestin** who will be joined in 2022 by a 2nd study engineer.

Innovative scientific AXIS

During its first decade, the IHU ICAN has implemented the necessary resources (technical, scientific and human) and developed an expertise to accelerate innovation in metabolic disease research. In 2021, the IHU ICAN strengthened its commitment to health data and imaging, in particular through the MAESTRIA project.
Indeed, with a wide spectrum ranging from basic research to patient care, the teams are mobilised to provide an answer to increasingly sophisticated questions on the collection, use and sharing of health data in research.



CARDIOMETABOLIC IMAGING

The ICAN imaging research team continues to develop new methods for advanced image acquisition and post-processing of cardiac, aortic, hepatic and adipose tissues. These methods are then made available to the Core Lab and the MRI acquisition platform.

Cardiac and aortic imaging includes assessment of morphology, function, hemodynamics (vortices and 4D flow MRI pressure gradients) and the characterisation of myocardial tissue. New algorithms offering mechanical functions and hemodynamic coupling indices have been developed. Imaging of the liver and adipose tissue focuses on the characterisation of the composition of the fiber-fatty tissues.

PUBLICATION

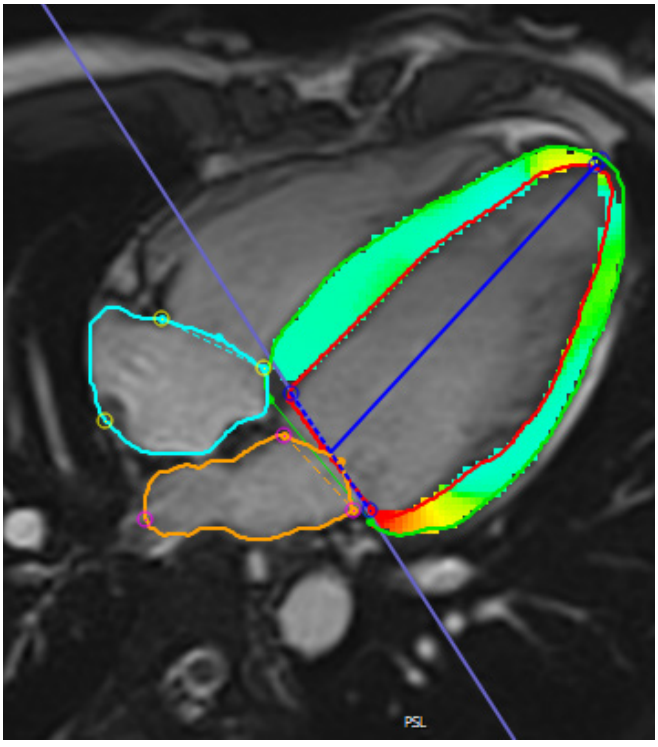
Abdominal adipose tissue components quantification in MRI as a relevant biomarker of metabolic profile. Bouazizi K, Zarai M, Dietenbeck T, Aron-Wisnewsky J, Clément K, Redheuil A, Kachenoura N. Magn Reson Imaging. 2021 Jul;80:14-20. PMID: 33872732

Our goals

- To demonstrate that myocardial, coronary and aortic alterations can be accurately detected and quantified by MRI as non-invasive diagnostic and prognostic biomarkers,
- To show the potential reversibility of these phenotypes by longitudinally monitoring hypercholesterolemic diabetic patients and early inflammatory and coronary pathologies,
- To improve stratification of the severity of CMD, and to identify shared pathways between different severity groups by identifying the subclinical alterations.

Alongside the clinical AXIS, that focus on innovative and sensitive imaging biomarkers, this axis also requires the integration of complex multilevel data and the design of multiparametric approaches to:

- Develop injection-free MRI methods
- Reduce the length of MRI examinations by optimising the acquisition and use of AI;
- Reduce image processing times via high-performance developments using artificial intelligence. This research has been undertaken in collaboration with the Sorbonne Centre for Artificial Intelligence (SCAI).



From among the 2021 publications, we would highlight the use of new software for quantifying fat in different tissues, particularly pericardial adipose tissue, which has enabled the definition of a new risk score for the progression to severe forms, for diabetic patients with COVID-19.

The abnormal accumulation of adipose tissue (AT) changes the metabolic profile and is a cause of cardiovascular complications. Traditional measures offered overall measures that did not enable the identification of the visceral and sub-cutaneous constituents. The aim of this study was to propose a new approach; to automatically quantify the amount and type of adipose tissue in the trunk via an MRI scan, in metabolic patients and control subjects. We were able to calculate a new organ fat infiltration index, "VAT", which enabled differentiation of the controls from the three metabolic patient groups (obese, metabolic syndrome or type 2 diabetic). In the future it could serve as a non-invasive predictor of cardiovascular complications in these patients.

Diabetic patients with COVID-19 have an accrued risk of severe forms, unrelated to their type of obesity. In these patients, the distribution of fats is characterised by an expansion of visceral and ectopic adipose tissues leading to systemic inflammation, which can play a role in driving the cytokine storm that is related to COVID-19 infections. Our goal was to determine whether adipose tissue around the heart, in combination with interleukin-6 levels, could predict the onset of short-term adverse events, death, and intensive care requirements, in diabetic patients with COVID-19 during the first 21 days following admission.
81 patients with type 2 diabetes, consecutively admitted for COVID-19, were included. On admission, interleukin-6 was measured, and a thoracic computed tomography (CT) with total cardiac adipose tissue index (CATi) measurement was taken. 25 % of patients died following in the aftermath of COVID-19, 25 % needed intensive care and 50 % were in conventional care 21 days after admission. Increased CATi and IL-6 levels were strongly linked to increased early mortality and the need for intensive care. These associations remained significant regardless of age, sex, BMI, or troponin-T levels, or the extension of lung lesions on the CT. The cardiac adipose tissue index and IL-6 determination at admission may help doctors better identify those diabetic patients at risk of developing potentially serious and life-threatening progression in the short term, irrespective of the obesity. These diabetic patients with elevated CATi on admission, a fortiori associated with high levels of IL-6, could constitute a relevant target population for which to rapidly initiate anti-inflammatory treatments.

PUBLICATION

Group Cardiac adipose tissue volume and IL-6 level at admission are complementary predictors of severity and short-term mortality in COVID-19 diabetic patients Cardiovasc Diabetol 2021. Phan F, Boussouar S, Lucidarme O, Zarai M, Salem JE, Kachenoura N, Bouazizi K, Charpentier E, Niati Y, Bekkaoui H, Amoura Z, Mathian A, Benveniste O, Cacoub P, Allenbach Y, Saadoun D, Lacorte JM, Fourati S, Laroche S, Hartemann A, Bourron O, Andreelli F, Redheuil A; COVID-19 APHPSU. Aug 12;20(1):165 PMID: 34384426

OTHER PUBLICATIONS

Epicardial and Pericardial Adiposity Without Myocardial Steatosis in Cushing Syndrome. Wolf P, Marty B, Bouazizi K, Kachenoura N, Piedvache C, Blanchard A, Salenave S, Prigent M, Jublanc C, Ajzenberg C, Droumaguet C, Young J, Lecoq AL, Kuhn E, Agostini H, Trabado S, Carlier PG, Fève B, Redheuil A, Chanson P, Kamenický P. J Clin Endocrinol Metab. 2021 Nov 19;106(12):3505-3514. doi: 10.1210/clinem/dgab556. PMID: 34333603.

Dysfunction in Children and Adolescents With Severe Obesity: A Cardiac Magnetic Resonance Imaging Myocardial Strain Study. Xu E, Kachenoura N, Della Valle V, Dubern B, Karsenty A, Tounian P, Dacher JN, Layese R, Lamy J, Ducou le Pointe H, Redheuil A, BlondiauxE. Multichamber. J Magn Reson Imaging. 2021 Nov;54(5):1393-1403. doi: 10.1002/jmri.27796. Epub 2021 Jun 21. PMID: 34155711.

Role of Cardiac Imaging in the Diagnosis of Immune Checkpoints Inhibitors Related Myocarditis. Ederhy S, Salem JE, Dercle L, Hasan AS, Chauvet-Droit M, Nhan P, Ammari S, Pinna B, Redheuil A, Boussouar S, Champiat S, Soulat-Dufour L, Cohen A. Front Oncol. 2021 May 13;11:640985. doi: 10.3389/fonc.2021.640985. PMID: 34055610; PMCID: PMC8158154.

MRI as a hallmark of tissue alteration in morbid obesity. Quant Imaging Med Surg. Bouazizi K, Zarai M, Marquet F, Aron-Wisnewsky J, Clément K, Redheuil A, Kachenoura N. Adipose tissue fibrosis assessed by high resolution ex vivo 2021 May;11(5):2162-2168. doi: 10.21037/qims-20-879. PMID: 33936996; PMCID: PMC8047361.

Prediction Model for Ventricular Arrhythmias in Arrhythmogenic Right Ventricular Cardiomyopathy. Baudinaud P, Laredo M, Badenco N, Rouanet S, Waintraub X, Duthoit G, Hidden-Lucet F, Redheuil A, Maupain C, Gandjbakhch E. External Validation of a Risk Can J Cardiol. 2021 Aug;37(8):1263-1266. doi: 10.1016/j.cjca.2021.02.018. Epub 2021 Mar 4. PMID: 33675936.

Myocardial fibrosis assessed by magnetic resonance imaging in asymptomatic heterozygous familial hypercholesterolemia: the cholcoeur study. Gallo A, Giral P, Rosenbaum D, Mattina A, Kilinc A, Giron A, Bouazizi K, Gueda Moussa M, Salem JE, Carrié A, Carreau V, Béliard S, Bittar R, Cluzel P, Bruckert E, Redheuil A, Kachenoura N. EBioMedicine. 2021 Dec;74:103735. doi: 10.1016/j.ebiom.2021.103735. Epub 2021 Dec 2. PMID: 34864619; PMCID: PMC8646177.

Quantitative magnetic resonance imaging measures of three-dimensional aortic morphology in healthy aging and hypertension. J Magn Reson Imaging. Dietenbeck T, Houriez-Gombaud-Saintonge S, Charpentier E, Gencer U, Giron A, Gallo A, Boussouar S, Pasi N, Soulat G, Mousseaux E, Redheuil A, Kachenoura N. 2021 May;53(5):1471-1483. doi: 10.1002/jmri.27502. Epub 2021 Jan 11. PMID: 33426700.

NEW INTERFACES IN CARDIOMETABOLIC DISEASES ROLE OF THE INTESTINAL MICROBIOTA IN CARDIOMETABOLIC PATHOLOGIES

Scientific objectives

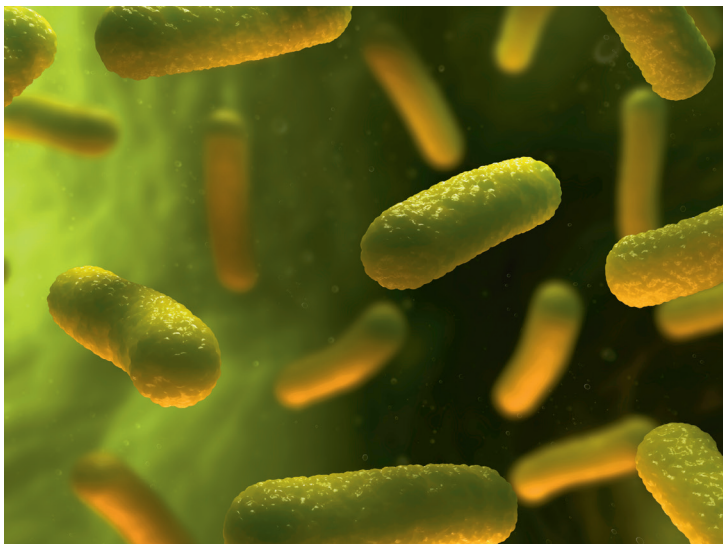
- To study the physiopathological role of the composition of the intestinal microbiota in the development of cardiometabolic diseases
- To identify intestinal microbiota biomarkers to improve prognoses or predict responses to drugs, and lastly,
- To establish proof of concept treatment studies to correct intestinal dysbiosis

PUBLICATION

Combinatorial, additive and dose-dependent drug-microbiome associations. Nature. Forslund SK, Chakaroun R, Zimmermann-Kogadeeva M, Markó L, Aron-Wisnewsky J, ; MetaCardis Consortium, Gøtze JP, Køber L, Vestergaard H, Hansen T, Zucker JD, Hercberg S, Oppert JM, Letunic I, Nielsen J, Bäckhed F, Ehrlich SD, Dumas ME, Raes J, Pedersen O, Clément K, Stumvoll M, Bork P. 2021 Dec;600(7889):500-505. PMID: 34880489

In 2021, some noteworthy publications resulted from major works

During the transition from a healthy state to cardiometabolic disease, patients are treated with multiple drugs, which leads to an increasingly disrupted intestinal microbiome and serum metabolome, which complicates the discovery of disease-specific biomarkers from the microbiota. Here, using integrated multi-omics analyses of 2,173 European subjects from the MetaCardis cohort, we showed that the explanatory power of drugs for variability in host and intestinal microbiome characteristics exceeds that of disease. We identified a relationship between taking cardiometabolic drugs, improved clinical markers, and microbiome composition, which supports the direct effects of the drugs. Taken together, our computational analysis untangles the effects of drugs and diseases on host and microbiome characteristics in multi-medicated individuals. Additionally, the robust signatures identified via our analysis provide new hypotheses for drug-host-microbiome interactions in cardiometabolic diseases.



PUBLICATION

Dendritic Cells Shape a Transmissible Gut Microbiota That Protects From Metabolic Diseases. Diabetes. Lécuyer E, Le Roy T, Gestin A, Lacombe A, Philippe C, Ponnaiah M, Huré JB, Fradet M, Ichou F, Boudebbouze S, Huby T, Gautier E, Rhimi M, Maguin E, Kapel N, Gérard P, Venteclef N, Garlatti M, Chassaing B, Lesnik P. Tolerogenic - 2021 Sep;70(9):2067-2080. PMID: 34078628

Excessive chronic contact between the microbiota and intestinal immune cells is known to trigger low-grade inflammation involved in numerous pathologies, such as obesity and diabetes. The significant bias of intestinal-adaptive immunity in the context of diet-induced obesity (DIO) is well described, but the way in which dendritic cells (DC's) participate in these changes is still poorly documented. To address this question, we subjected transgenic mice with increased DC lifespan and immunogenicity (DChBcl-2 mice) to a diet rich in obesogenic fats (DIO). These mice showed resistance to diet-induced obesity and metabolic alterations, improved intestinal barrier function and lower intestinal inflammation. Analyses of the composition and function of the microbiota reveal that the microbiota of these mice is characterised by weaker immunogenicity and increased butyrate production. Faecal microbial transplantation experiments were shown to be enough to transfer obesogenic diet resistance status to wild-type mice, demonstrating that maintaining the tolerogenic capacity of DC's results in a microbiota capable of driving obesity resistance. The tolerogenic function of the DC's is emerging as a powerful new target in the management of metabolic diseases.

Pathologies linked to lipid storage disorders

Abnormal storage of lipids is associated with obesity, lipodystrophies (LD) and NASH (Non-Alcoholic SteatoHepatitis), and is likely to share common signalling pathways, in particular miRNAs, dihydroceramides, necroptosis, autophagia, fibrosis and inflammation. There is a critical need for new biomarkers that go beyond the baseline BMI (body mass index) to improve the phenotyping, prognosis and diagnosis of these lipid storage-related diseases.

The IHU teams have just identified a new biomarker

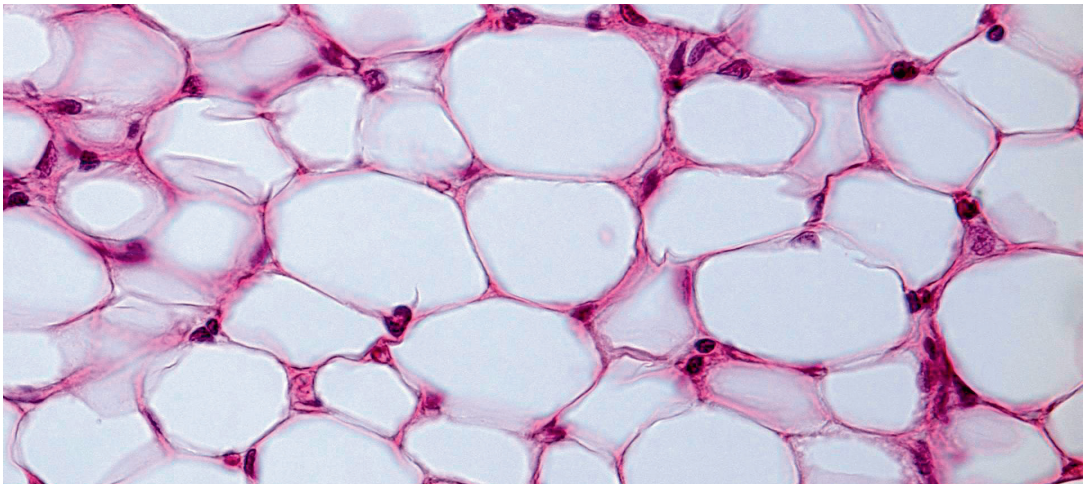
While low levels of high-density lipoprotein cholesterol (HDL-C) are a well-established cardiovascular risk factor, an extremely high rate of HDL-C is paradoxically associated with high cardiovascular risk, resulting in a U-shaped relationship with cardiovascular disease. It was reported recently that the transfer of free cholesterol to HDL during lipolysis of triglyceride-rich lipoproteins (TGRL) underlies this relationship, linking HDL-C to triglyceride metabolism and atherosclerosis. In addition to free cholesterol, other surface components of TGRL, primarily phospholipids, are transferred to HDL during lipolysis.

In all the populations tested (low HDL-C with acute myocardial infarction, with Tangier disease or with type 2 diabetes, elevated HDL-C and very high HDL-C), the ability of HDL to acquire the fluorescent phospholipid was directly correlated with HDL-C. No relationship between the ability of the HDL to acquire the tracer and overall and cardiovascular mortality obtained from epidemiological studies for the mean levels of HDL-C observed in the study populations was obtained.

These data indicate that the ability of HDL to acquire phospholipids from TGRL during LPL-mediated lipolysis is proportional to HDL-C and does not reflect cardiovascular risk in subjects with widely differing HDL-C levels.

PUBLICATION

Phospholipid transfer to high-density lipoprotein (HDL) upon triglyceride lipolysis is directly correlated with HDL-cholesterol levels and is not associated with cardiovascular risk. ***Atherosclerosis.*** Ma F, Darabi M, Lhomme M, Tubeuf E, Canicio A, Brerault J, Medadje N, Rached F, Lebreton S, Frisdal E, Brites F, Serrano C, Santos R, Gautier E, Huby T, El Khoury P, Carrié A, Abifadel M, Bruckert E, Guerin M, Couvert P, Giral P, Lesnik P, Le Goff W, Guillas I, Kontush A. 2021 May;324:1-8. PMID: 33798922



Myocardial metabolism and cardiomyopathies

Myocardial metabolism is an emerging cardiometabolic interface, which could be of particular interest in cardiomyopathies. In fact, the heart is characterised by a higher oxidative rate than other organs, and is able to use different substrates (myocardial flexibility), with variable energy output. How this metabolic flexibility could contribute to the development of cardiomyopathy and cardiac insufficiency, and whether this aspect could be of potential therapeutic interest, remain unanswered questions.

A new study by IHU teams has opened up new leads on the links between metabolic disorders and cardiac electrical disorders

PUBLICATION

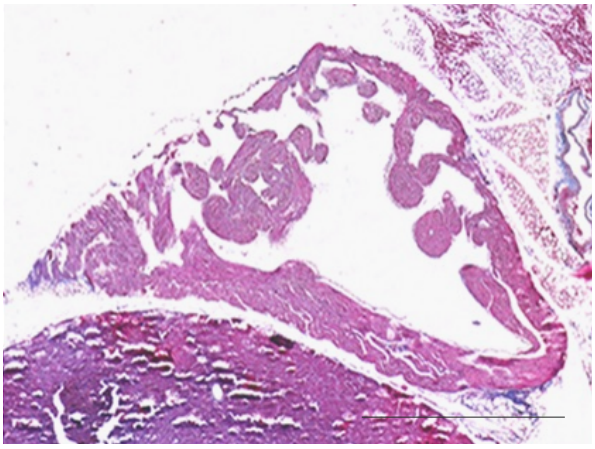
Impacts of a high fat diet on the metabolic profile and the phenotype of atrial myocardium in mice. Cardiovasc Res. Suffee N, Baptista E, Piquereau J, Ponnaiah M, Doisne N, Ichou F, Lhomme M, Pichard C, Galand V, Mougenot N, Dilanian G, Lucats L, Balse E, Mericskay M, Le Goff W, Hatem S. 2021 Dec 31:cvab367. PMID: 34971360

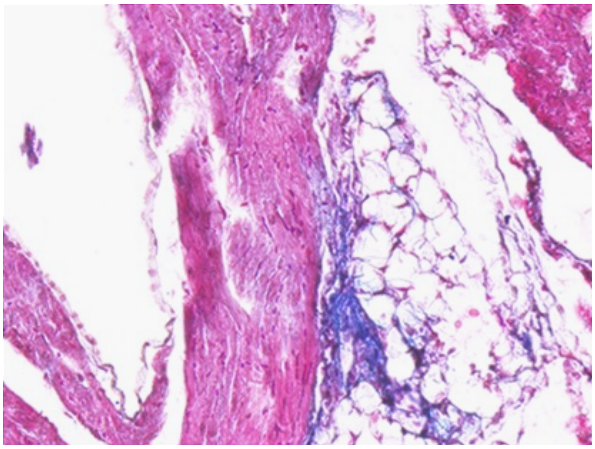
Obesity, diabetes and metabolic syndromes are risk factors for atrial fibrillation (AF). We tested the hypothesis that metabolic disorders have a direct impact on the atria, promoting the formation of the AF substrate. A non-targeted metabolic and lipidomic assessment was used to study the consequences of a prolonged high-fat diet (HFD) on the atria of mice. After 16 weeks of a HFD, the obesogenic mice showed vulnerability to AF. The HFD diet transforms energy metabolism, as shown by the metabolomic and lipidomic analysis, causes fat accumulation and induces electrical remodelling of the atrial myocardium of the mice, which then become vulnerable to AF.

Translational perspective

Understanding the link between metabolic diseases and atrial fibrillation is of significant importance. One hypothesis suggests that in addition to common comorbidities, metabolic disorders promote the substrate of atrial fibrillation. Here we show that after a prolonged high-fat diet, the atrial myocardium becomes adipogenic, inflamed and vulnerable to atrial fibrillation. This tissue remodelling appears to result from an imbalance between the absorption and oxidation of fatty acids, leading to storage of long-chain lipids, the activation of metabolically sensitive potassium channels and a shortening of the action potential. Consequently, dietary regime seems to be an important link between metabolic disorders and atrial fibrillation.

HFD impacts atrial structure





RARE DISEASES

The studies carried out on patients with rare cardiometabolic diseases aim to improve the treatment and care of these patients, and also to better understand frequent chronic cardiometabolic diseases and to identify new therapeutic avenues, as shown by the results of two new studies published by the IHU ICAN teams.

PUBLICATION

Genome-wide association analysis in dilated cardiomyopathy reveals two new players in systolic heart failure on chromosomes. Garnier S, Harakalova M, Weiss S, Mokry M, Regitz-Zagrosek V, Hengstenberg C, Cappola TP, Isnard R, Arbustini E, Cook SA, van Setten J, Calis JJA, Hakonarson H, Morley MP, Stark K, Prasad SK, Li J, O'Regan DP, Besse C, Fontaine V, Blanché H, Ader F, Keating B, Curjol A, Boland A, Komajda M, Cambien F, Deleuze JF, Dörr M, Asselbergs FW, Villard E, Trégouët DA, Charron P. - 3p25.1 and 22q11.23 Eur Heart J. 2021 May 21;42(20):2000-2011. PMID: 33677556

Our objective was to better understand the genetic premises of dilated cardiomyopathy (DCM), one of the primary causes of systolic cardiac insufficiency.

We conducted the largest genome-scale association study on DCM to date, with 2,719 cases and 4,440 controls. We identified and replicated two new loci associated with DCM on chromosome 3p25.1 and chromosome 22q11.23, while confirming two previously identified DCM loci on chromosomes 10 and 1, BAG3 and HSPB7. A genetic risk score constructed from the number of risk alleles at these four DCM loci revealed a 3-fold increased risk of DCM in individuals with 8 risk alleles compared to individuals with 5 risk alleles (the median for the reference population). In silico annotation and functional sequencing analyses on iPSC-derived cardiomyocytes identified SLC6A6 as the most likely DCM gene at the 3p25.1 locus. This gene codes for a taurine transporter that has been shown to be involved in myocardial dysfunction and DCM in numerous human and animal observations. At the 22q11.23 locus, in silico annotations and data mining, and to a lesser extent functional analysis, strongly suggest SMARCB1 as the responsible candidate gene.

This study enables a better understanding of the genetic architecture of DCM and highlights new biological pathways underlying cardiac insufficiency.

PUBLICATION

Generation of a heterozygous SCN5A knockout human induced pluripotent stem cell line by CRISPR/Cas9 Gizon M, Duboscq-Bidot L, El Kassar L, Bobi n P, Ader F, Giraud-Triboult K, Charron P, Villard E, Fontaine V, Neyroud N. edition.Stem Cell Res. 2022 Apr;60:102680. PMID: 35093717

Mutations leading to haploinsufficiency in SCN5A, the gene coded for the Nav1.5 subunit of the cardiac sodium channel, are implicated in potentially life-threatening cardiac disorders. Using CRISPR/Cas9-mediated genome editing, here we generated a human induced pluripotent stem cell (hiPSC) line carrying a heterozygous mutation in exon 2 of SCN5A, which leads to the appearance of a premature stop codon. The SCN5A-clone 5 line maintained a normal karyotype, morphology and pluripotency, and differentiated into the three germlines. These hiPSC-derived cardiomyocytes provide a useful model for studying channelopathies associated with heterozygous SCN5A deficiency.

COVID-19 AND METABOLIC DISEASES

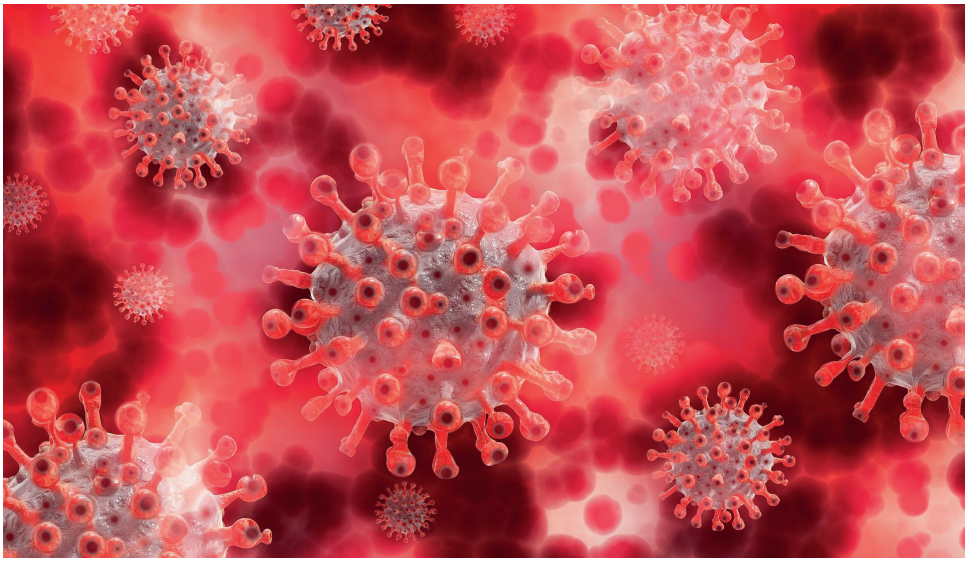
The IHU ICAN was strongly involved from the beginning of the Cov-2 SARS epidemic, in clinical care through to research. Thanks to the reactivity of the IHU ICAN and with the help of our founders, in particular the AP-HP, it has been possible to carry out projects aimed at studying the indirect impact of COVID-19 on the treatment and care of cardiometabolic diseases and also to study new prognostic models of aggravation of the disease.

STRAT-COVID Study

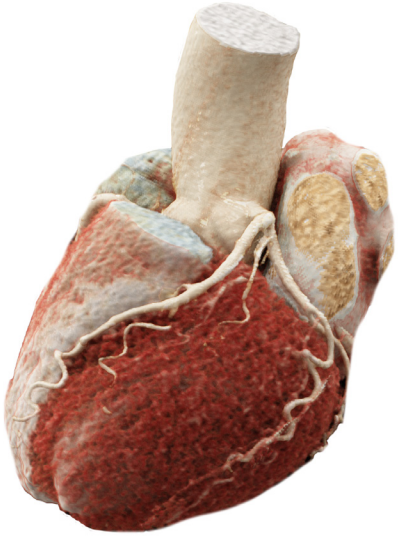
The IHU ICAN has been selected by the AP-HP Foundation for the STRAT-COVID project, which proposes to develop and validate the prognostic performances of a predictive model for the onset of a severe form of the infection during hospitalisation for COVID-19. The model will be based on the initial characteristics of patients who do not immediately present with a severe form of the infection, and will seek to predict the risk of progression to a severe form using a multiparametric approach: clinical, metabolomic, lipidomic, and based on cellular immunity biomarkers and cardiothoracic imaging data.

COVIPIED Study

The network of clinicians led by Dr Georges Ha Van also received ICAN's support for the implementation of a project on the impact of the 1st coronavirus/COVID pandemic quarantine on the healing time of foot chronic wounds. Also, the mandatory quarantine period related to the COVID 19 pandemic (in France from 17/03/20 to 11/05/20), which limited patients' outings from home and therefore walking distances prompts the following questions:
Could that have had a beneficial effect on wound repair times?
Or on the contrary, could it have led to a higher rate of complications because of the absence of appropriate treatment caused by patients seeing their doctors so much less during that period? The year 2021 was devoted to the meticulous retrieval of pseudonymised data from the recruiting centres and the creation of a global database of all patients.



Flagship and structural projects



CARDIOVASCULAR IMAGING

MAESTRIA, Machine Learning and Artificial Intelligence for Early Detection of Stroke and Atrial Fibrillation

Coordinator: **Prof. Stéphane Hatem, director of the IHU ICAN and the Inserm UMR_S1166 research unit at the Sorbonne University**

Atrial fibrillation (AF) is the most common cardiac rhythm disorder and the primary cause of cerebral vascular accidents (CVA). Frequently associated with cardiac insufficiency, arterial hypertension and also obesity and diabetes, it affects about 1% of the general population and up to 8% of people over 80. The current challenge in the clinical treatment and care of AF is to intervene before the onset of arrhythmia, in other words at the first signs of atrial cardiomyopathy. That is the goal of the MAESTRIA project (Machine Learning and Artificial Intelligence for Early Detection of Stroke and Atrial Fibrillation), a highly innovative research project that has brought together 18 partners from Europe, the United States and Canada.

In France, close to 750,000 people have atrial fibrillation and it is estimated that the number of cases annually is between 110,000 and 230,000. Its frequency and prevalence are growing rapidly, mainly because of the ageing population. The increase in the number of people with AF comes with a high cost for the health care system, estimated at around €2.5 billion. Understanding and preventing this pathology therefore represents both a medical challenge and an economic one.
MAESTRIA aims to develop and validate the first digital platform for the integrative diagnosis of atrial cardiomyopathy. By combining multimodal imaging data with patients' physiological data (omics, clinical, etc.), this platform will be able to identify new treatment targets for improved diagnostic accuracy. It will increase the efficacy and efficiency of treatment by better preventing the complications of atrial cardiomyopathy, such as atrial fibrillation and cerebrovascular accidents, two significant health problems.

This project is centered on three strategic AXIS

> Personalised diagnosis and innovative, pluridisciplinary treatment plans

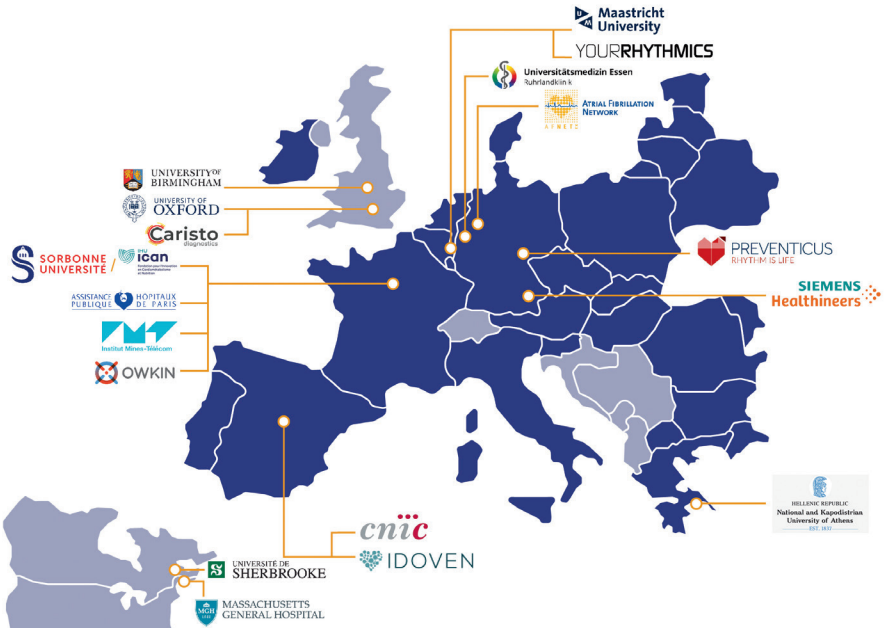
Through the combined use of genomic, metabolic and tissue inflammation research data. The analysis of these data, which are involved in the progression of the disease, will make it possible to establish a personalised diagnosis and to define an innovative multidisciplinary patient circuit.

>Risk stratification

In patients with AF: the use of artificial intelligence will permit the reading and analysis of a large amount of imaging data in order to define each patient's risk of seeing their disease develop into a CVA. Risk stratification allows new treatment strategies to be offered.

> Deployment of a pan-European digital diagnosis platform

MAP OF MAESTRIA CONSORTIUM



Partners

The MAESTRIA consortium comprises 18 partners:

- **12 academic institutions** heavily focused on clinical research data and integration, and artificial intelligence: Sorbonne University, Assistance Publique des Hôpitaux de Paris, Oxford University, Birmingham University, AFNET, Essen University, Maastricht University, Athens University, CNIC, Massachusetts General Hospital, IMT Transfert, Sherbrooke Research Centre at the Sherbrooke University Hospital Center
- **5 biotech companies (SME):** Caristo Diagnostics Limited, Owkin, Idoven, Preventicus, YourRhythmics
- **1 large imaging company:** Siemens Healthcare

The project launch took place in the presence of all the partners on the Pierre and Marie Curie campus at Sorbonne University on the 27th and 28th of September 2021 (See highlights p. 26).

MAESTRIA

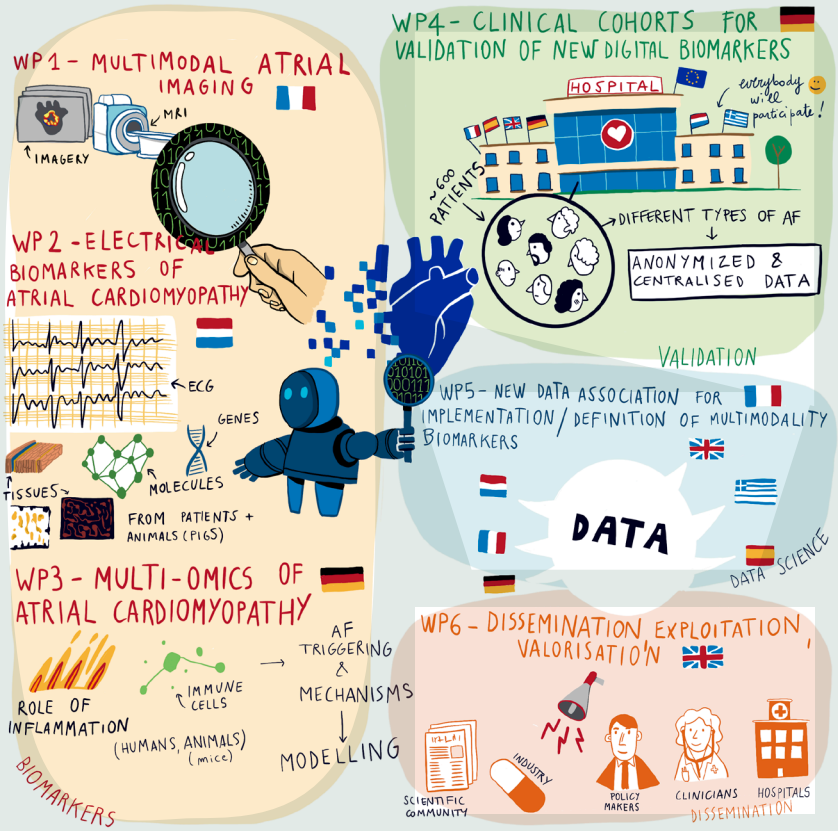
Health data, a significant challenge for MAESTRIA

The MAESTRIA project is the first large-scale IHU project dealing with the research and development of AI solutions for diagnostic and predictive assistance systems. These kinds of projects, which require wide access to patients' health data, raise immediate issues of compliance with regulations on the protection of personal data (in particular the GDPR and the French Data Protection Act) as well as more general ethical questions on the place of different expertises within the context of the development of predictive tools in medicine, data governance and patient information.

Data exchanges between the 18 partners is planned: clinical and raw data will be collected by the sponsors or study managers. This raw data are transferred, in pseudonymised form, to corelab experts in various fields of analysis (MRI, ultrasound, ECG etc.) for the training of artificial intelligence algorithms. The results of the corelabs analysis are then fed back into each study's clinical database. In the second phase of the project, the integration of complex and heterogeneous data from the first phase of the project, using traditional statistical tools and/or new AI developments, will be carried out in a collaborative manner, in order to identify new signatures or predictive markers for atrial fibrillation and CVA's. Each consortium partner's data scientists have worked on implementing data standardisation, to ensure that it is shared and circulates smoothly.

This type of project needs significant exchanges of health data in a regulatory context that is only partially uniform within Europe. In fact, some of the regulations differ between European countries, both in respect of sensitive personal data and protecting participants in clinical studies. For example, the GDPR, which set out requirements for pseudonymised health data, has been reinforced by French law and have to be properly implemented in international consortia. It is also a matter of implementing relatively new legal concepts (co-

> **THE MAESTRIA PROJECT IS VERY ENCOURAGING.**
>
> Maud Decraene



responsibility for processing, transfers outside the EU, anonymisation) which are assessed differently by each institution from the perspective of their risk management policy. Finally, the use of data in the development of AI raises issues of intellectual property and fair compensation for the data producers, who invest heavily in the production of healthcare data. The question also arises for the users of the models that result from the project, for whom there is still a long way to go before they can draw profits from their innovations.

The MAESTRIA project is very encouraging. It prioritises innovation, creativity and collaborative work between all the consortium's teams that are involved, irrespective of their areas of expertise: medical, scientific, legal, regulatory, etc.

The project includes numerous data transfers from existing and prospective studies, specifically designed to meet the needs of developments in AI.

Through an agile approach, the IHU hopes to support an international scientific community with increasingly ambitious projects, while complying with the protection of personal data. Challenges to be addressed include: the ability to explain how the data will be used to the regulatory authorities or ethics committees of the various health data repositories already in place, pseudonymisation of standard imaging data from treatment and care, issues of interoperability and standardisation of variables and data formats. The ways in which patients are informed also vary greatly between countries due to the partial standardisation of data protection and the regulatory context of clinical trials within the EU.

Another aspect of the complexity of the project comes from the fact that the partners use different expert structures to collect, centralise, store and use the medical data. Each structure has implemented strict rules, in compliance with their national legislation, to ensure the safety of the data. However, these rules can act as an obstacle to the circulation of data in a clinical research context, which requires the processing of pseudonymised data. And the IT systems needed for machine learning require a

computing power that is not available in health data warehouses.
All the data governance defined for Maestria has been formalised, in the consortium agreement and the specific contracts for data exchange between partners.
In conclusion, the key words for the work done are transversality and excellence.
In addition to the integration of scientific and medical data, the MAESTRIA project enables integration of expertise within the IHU and between partners in agile mode.
The IHU works directly with Teralab (the infrastructure that hosts the data hub), the AP-HP, Oxford and AFNET (sponsors and managers of the studies), the corelabs (MRI, Echo, Holter etc.) and Idoven, Owkin Siemens. We have also been able to rely on the valuable expertise of the SCAI teams in the field of AI on several occasions.
Maestria is a project representative of the IHU's research. We had to organise ourselves and develop certain resources as a precursor to the direction taken by our IHU, as a pilot player in this type of ambitious and international research, which needs data governance adapted to the scientific challenges, while respecting ethical rules.

MAESTRIA IS A PROJET REPRESENTATIVE OF THE IHU'S RESEARCH."

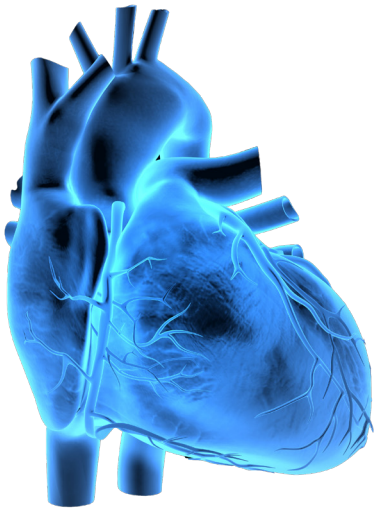
Stéphane Hatem

**The key words for the work done are transversality and excellence.
As with the research teams, the IHU's support functions have adapted their way of working in partnership with the scientific, IT and medical teams. In addition to the integration of scientific and medical data, the Maestria project has induced the integration of expertise within the IHU and between partners in agile mode."**

Maud Decraene
Manager of the Legal, Compliance and Data Policy Unit

THE OPTIM STUDY AIMS TO DEFINE NEW IMAGING MARKERS AS DECISION SUPPORT TOOLS FOR THE USE OF IMPLANTABLE AUTOMATIC DEFIBRILLATORS TO PREVENT SUDDEN DEATH."

Prof. Alban Redheuil

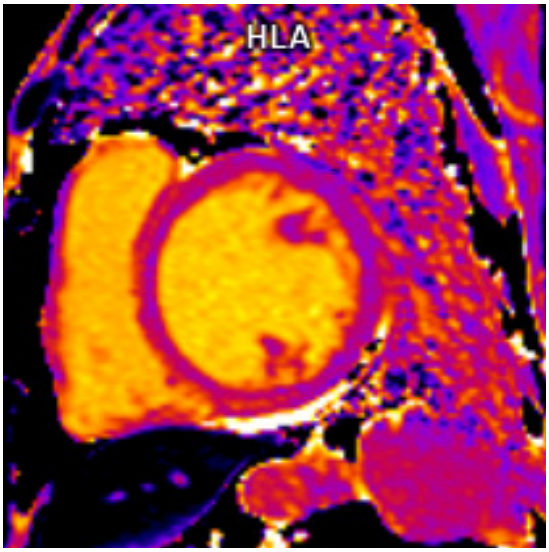


OPTIM: to define new imaging markers as decision support tools for the use of implantable automatic defibrillators to prevent sudden death

Coordinator: **Prof. Alban Redheuil, PU-PH, scientific manager ICAN Imaging / Nadjia Kachenoura DR Inserm U1146, Manager, Cardiovascular Imaging Team, Biomedical Imaging Lab**

Hypertrophic cardiomyopathy (HCM) is a genetic disease, generally autosomic dominant, with a prevalence of ~1/500 in the general population. HCM represents a significant cause of sudden death of a cardiac origin (SDC) in young people, and is the primary cause of SDC in athletes under the age of 35. The only effective prevention of SDC, besides restricting exercise, is the use of implantable automatic defibrillators (IAD's). Keeping in mind the potentially lethal prognosis of HCM, identifying patients who could benefit from an IAD is fundamentally important. However, while the indication for IAD's in secondary prevention is confirmed in the USA and in Europe the indication in primary prevention is still debated. Further, the current recommendations are all based on retrospective studies and have significant limitations, including the poor predictive performance of the characteristics on which they are premised, the failure to take recently identified risk markers into account, the arbitrary threshold for implantation, the lack of consideration of the adverse effects of defibrillators and the absence of any medical-economic evaluation. Overall, the current situation calls for a significant improvement in estimating individual risk and tools for making medical decisions in respect of this disease.

The OPTIM study aims to define new imaging markers as decision support tools for the use of implantable automatic defibrillators to prevent sudden death. One of the central goals of this project, which is going to generate a large number of imaging biomarkers, will be a pragmatic approach based on the clinical utility of these biomarkers. This approach consists of systematically testing simple and easily accessible parameters, through to the most complex ones, in order to determine the real incremental prognostic value of the most methodologically demanding approaches. This work will enable the risk score to evolve, by validating the use of the latest imaging techniques in the risk stratification of hypertrophic cardiomyopathies.



CARDIOLOGY

The year 2021 was a particularly important period in respect of an intensified collaboration between the IHU ICAN and the thoracic surgery department. The two clinical studies from the PSPC CALYPSO project - ECPELLA and IMPULSMACS - were able to start, and to recruit their first patients.

PSPC CALYPSO

Heart failure is implicated in one death in every ten in France. This chronic disease is often fatal, with close to one patient in every two dying in the five years following their diagnosis. The number of patients affected by heart failure is growing as the population ages and becomes more sedentary.

There are constant treatment innovations in the area of heart failure, and have led to improved prognoses and better quality of life for the patients. For those with terminal heart failure, a heart transplant remains the main treatment solution. But on the one hand, the number of available transplants is insufficient for the number of transplant candidates, and on the other hand, heart transplantations are associated with risks of rejection, infections and cancers, with a current median survival of 12 years. Thus heart transplants cannot be the universal treatment solution for heart failure.

Alternative treatment to heart transplants

An LVAD implant is a medium to long-term treatment option for patients with terminal heart failure and isolated left ventricular dysfunction.

An LVAD (Left Ventricular Assist Device) is a medical device whose role is to help the heart by doing the work normally done by the left ventricle.

Nevertheless, the use of these devices remains limited due to the frequency of their - mostly unpredictable - adverse effects. Several factors, including pulsatility, have been associated with LVAD complications in the literature, in particular with haemorragic complications.

A breakthrough technology to meet a public health challenge: chronic heart failure.

The CALYPSO program aims to optimise and then clinically validate the “CorWave LVAD” device, an implantable total cardiac assistance with physiological behaviour, i.e. restoring real

pulsatility, with the objective of reducing the risk of complications associated with existing LVAD's.

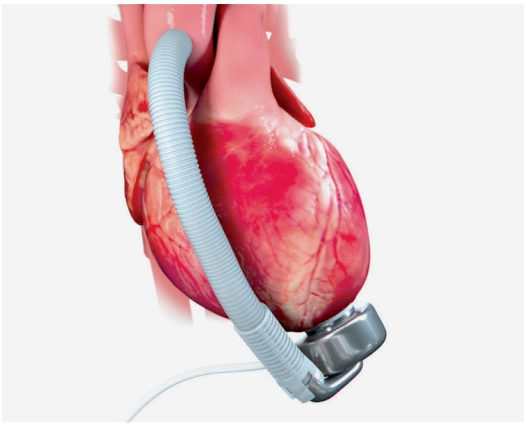
> ECPELLA

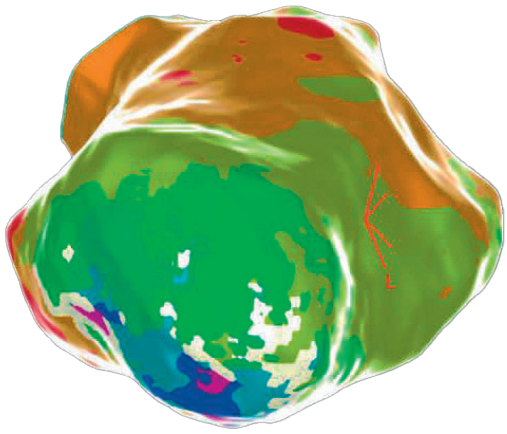
The aim of the study is to evaluate the clinical, biological, haemodynamic and echocardiographic criteria in patients undergoing venous-arterial ECMO (extracorporeal membrane oxygenation) that are associated with the absence of the development of right cardiac insufficiency when switched to IMPELLA®. IMPELLA® is a circulatory assistance system that pumps blood from left ventricular cavity and continuously ejects it into the aorta.
We are looking to establish a predictive score for dysfunction in a patient within 48 hours of weaning from the ECMO following IMPELLA® placement. This will make it possible to broaden the indication for LVAD implants, which is less cumbersome than performing a transplant or implanting an artificial heart.

> IMPULSMACS

This project aims to evaluate the association between pulsatility and complications in patients with an LVAD implant, in particular thrombotic and haemorragic complications. Pulsatility can be preserved when the left ventricle is able to eject, despite circulatory support. This pulsatility is a left ventricular function-related pulsatility that generates a pulse wave with its own aortic valve opening, different from the weak pulsatility generated by medical devices.
The hypothesis of this study is that preserving this circulatory pulsatility in patients wearing LVADs has a potential beneficial effect on reducing significant complications associated with using an LVAD.
The study will monitor the patients on a monthly basis during the 6 months following implantation of their LVAD in order to identify, as early as possible, the appearance of possible adverse effects (severe postoperative gastrointestinal bleeding, right ventricular failure beyond 24 hours, platelet dysfunction, postoperative CVA, immune/inflammatory reaction etc.).

In parallel, two other industry-sponsored projects have been set up with the IHU ICAN as a third-party structure.
The first project is an interventional trial of XVIVO, which aims to demonstrate the performance of a new cardiac graft transport system. The surgery department at Pitié-Salpêtrière is the first centre in terms of patient recruitment, with 20 graft patients included in 2021.
The second project is the CARMAT artificial heart project (EFICAS trial).





RHYTHMOLOGY

CATS-AF

Coordinator: **Dr Nicolas BADENCO, Rhythmology Unit at the Institute of Cardiology, Pitié-Salpêtrière Hospital.**

This study is part of the MAESTRIA project. Atrial fibrillation (AF) is the most common rhythm disorder in Europe and incidence rates are growing as the population ages. This pathology develops progressively, initially with paroxysmal arrhythmia attacks that become persistent and then permanent. It frequently forms part of a cardio-metabolic context and is associated with elevated morbidity and mortality. The progression to these different stages is difficult to predict, but correlates to a remodelling of the atrial myocardium constituting atrial cardiomyopathy. The mechanisms are complex and the condition is poorly characterised in clinical practice. Treatment of AF comprises 2 AXIS: prevention of cardio-embolic risk and rhythm control. The therapeutic options for this control are antiarrhythmic drugs and, above all, catheter ablation, an interventional cardiology technique that consists of treating the areas responsible for the initiation and perpetuation of the AF, by applying radiofrequency energy or cryotherapy to the myocardial tissue. The efficacy of this treatment is in the order of 75% at 1 year.

The study focuses on patients who are less than 60 years old with symptomatic atrial fibrillation, for whom treatment with catheter ablation is proposed in accordance with current international recommendations. We will be able to observe early changes in the disease in these young patients, in order to characterise the damage to the atrial myocardium as early as possible.
The principal objective, in collaboration with the ICT cardiovascular imaging teams of PSL/ICAN/LIB and Bordeaux Radiology/ Lyric, is to evaluate the association between regional and global myocardial (strain) abnormalities by magnetic resonance imaging, and the amplitude of the atrial intracardiac electrical potential measured during the catheter ablation procedure, in young subjects with symptomatic atrial fibrillation. The combined analysis of regional electrophysiological, morphological and functional parameters of the left atrium could improve early detection of atrial cardiomyopathy and predict the recurrence of atrial fibrillation.

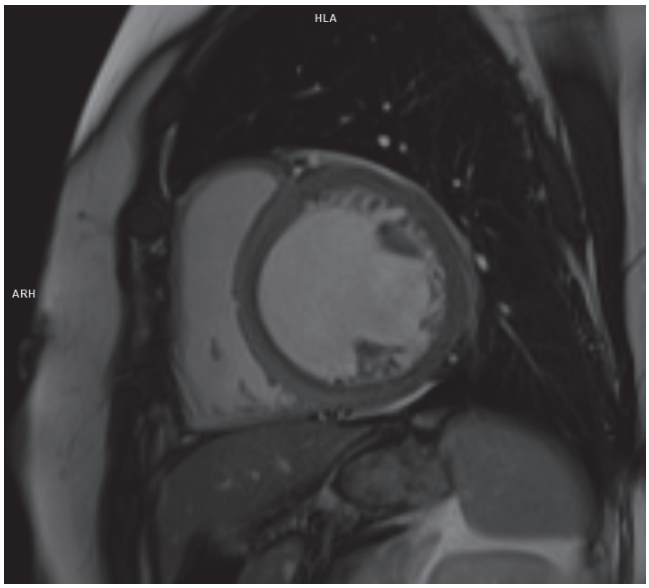
CT-AF

Coordinators: **Prof. Estelle GANDJBAKHCH, head of the Rhythmology Unit at the Institute of Cardiology, Pitié-Salpêtrière Hospital/ Dr Mikael LAREDO, Rythmology Unit, Pitié-Salpêtrière Hospital / Dr Hubert COCHET, radiology department and diagnostic and interventional imaging, Bordeaux IHU Liryc**

Atrial fibrillation (AF) ablation is a benchmark interventional treatment for patients presenting with symptomatic AF refractory to medical therapy. The known predictive success factors for the procedure are currently insufficient to appropriately select those patients who could draw the most benefit from this invasive procedure. Previous studies have shown that quantification of atrial fibrosis with magnetic resonance imaging (MRI) would be a good marker of atrial remodelling that would reliably predict the success of the ablation procedure. However, routine use of this technique is very limited because of the complexity of the quantitative analysis and the limits of spatial resolution. The link between epicardial fat fibrosis and the arrhythmogenic process has been established, notably by the IHU ICAN teams. CT, which is also routinely used to study atrial anatomy before AF ablation, could be used to characterise epicardial fat in the patient, and thus be a relevant substitute for directly characterising fibrosis. Thus, in addition to anatomical assessment, the study of epicardial fat using cardiac CT could be an interesting approach for evaluating the AF substrate.

The evaluation of cardiac fat can be done using several techniques: ultrasound, CT or MRI. However, there is considerable heterogeneity between techniques in respect of the identified fat target, which can be sub-epicardial, epicardial or pericardial in location. The post-processing of images from these imaging modalities remains poorly automated and tedious (several hours of analysis are required using the reference techniques), limiting their impact in clinical practice. In the context of research carried out in the biomedical imaging laboratory, new atrial imaging tools have been developed: software for the automatic analysis of left atrial epicardial fat in CT and functional analysis of the left atrium with strain measurement.
The principal objective of this study is to assess the prognostic value of a new automated technique of volumetric measurement of atrial intra myocardial fat on cardiac CT, and to measure the left atrial global strain on MRI in patients who are candidates for a first AF ablation.

These techniques, in particular the automated measurement of left atrial fat on CT, if validated in clinical practice, would allow a simple assessment with no additional costs,



of the arrhythmogenic substrate in AF, with cardiac CT as part of the routine evaluation before any ablation procedure to study the anatomy of the left atrium. Finally, the longitudinal nature of this study with the measurement of post-ablation residual sub-epicardial fat volume could enable a determination of the impact of the ablation procedure on fat remodelling, and its link to successful procedures, as was recently suggested in a study on myocardial MRI. In that study, post-ablation residual fibrosis is a significant predictive factor in the risk of recurrence (Akoum, Morris, et al. 2015).

"THE VALIDATION OF A SIMPLE AND REPLICABLE IMAGING TECHNIQUE TO PREDICT SUCCESSFUL ABLATION WILL PROVIDE A USEFUL TOOL TO PRACTITIONERS FOR OPTIMISING THE SELECTION OF CANDIDATE PATIENTS."

Prof. Estelle Gandjbakhch

The validation of a simple and replicable imaging technique for the prediction of ablation success would provide practitioners with a useful tool when selecting patients for this procedure, and when choosing its technical modalities.

ACORE

Coordinator: **Prof. Estelle GANDJBAKHCH, head of the Rhythmology Unit at the Institute of Cardiology, Pitié-Salpêtrière Hospital**

Arrhythmogenic cardiomyopathy (AC) is an inherited cardiomyopathy responsible for severe ventricular rhythm disorders that can lead to sudden death or cardiac insufficiency. This pathology was first described in 1982 by our hospital group. Historically, the cardiology department at the Pitié Salpêtrière hospital has been one of the primary French recruitment centres for this pathology. A long active lineup of patients with this pathology is or has been monitored in our department (more than 500 patients since 1982).

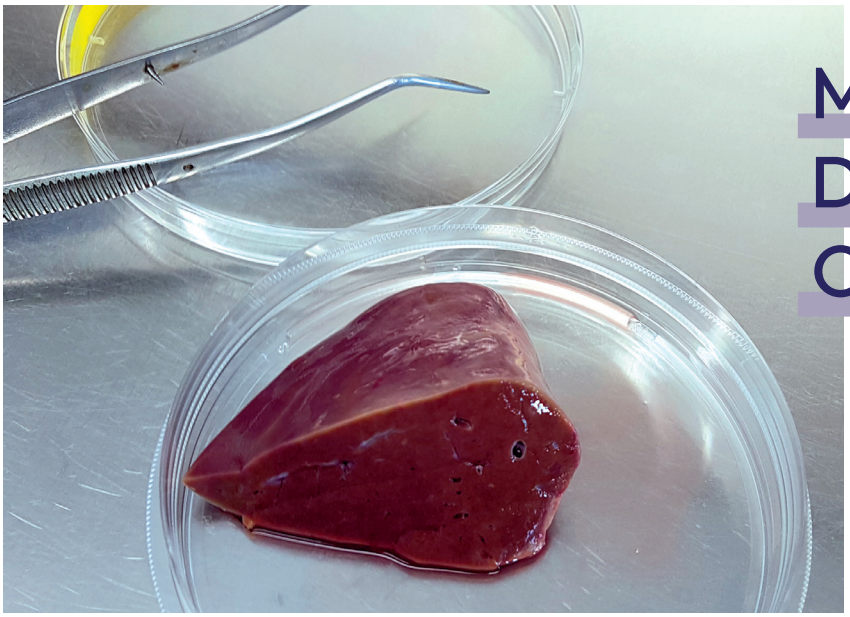
This pathology is characterised by the development of fibro-fatty deposits within the right and left ventricular myocardium, which form areas of arrhythmogenic substrate and cause progressive right ventricular dilatation culminating in heart failure.

The physiopathology of AC and the origin of the development of fibro-fatty deposits are still not well understood. *In vitro* studies have suggested the involvement of the wnt/beta-catenin pathway, involved in fibro- and adipo-genesis. Ionic remodelling was also observed. The disease can also present in the form of myocardial inflammatory flare-ups, which can sometimes reveal the disease. This type of presentation appears to be more common in AC than in other cardiomyopathies. Although for the time being, the origin of these inflammatory phenomena remains unexplained, several hypotheses have been proposed, such as an increased susceptibility to cardiotropic viruses or autoimmune phenomena that could be triggered by the presence of desmosomal mutations. In support of that latter hypothesis, recent research has identified anti-DSG2, anti-junction and anti-heart autoantibodies in patients. This autoantibodies have a diagnostic and prognostic value but also play a direct role in the physiopathology of the disease, in particular the inflammatory phenomena. Inflammatory phenomena that could have a direct link to the formation of the fibro-fatty infiltrates, which are a source of ventricular arrhythmias and ventricular dysfunction.

In addition, despite recent advances in the diagnosis, genetics and prognosis of this pathology, many problems remain concerning diagnosis and prognostic stratification. AC remains an hereditary cardiomyopathy for which making a diagnosis is the most difficult, because there are no specific clinical or imaging criteria. Identifying new diagnostic biomarkers is therefore a significant challenge in this pathology. From that perspective, the identification of specific markers linked to auto-immunity would be a major breakthrough. Similarly, the identification of prognostic biomarkers would give clinicians new tools with which to improve treatment and care of the disease.

In the context of this study, the population of interest comprises all adult patients presenting with a clinical phenotype of arrhythmogenic cardiomyopathy or who carry a mutation that puts them at risk of AC, regardless of the clinical phenotype.

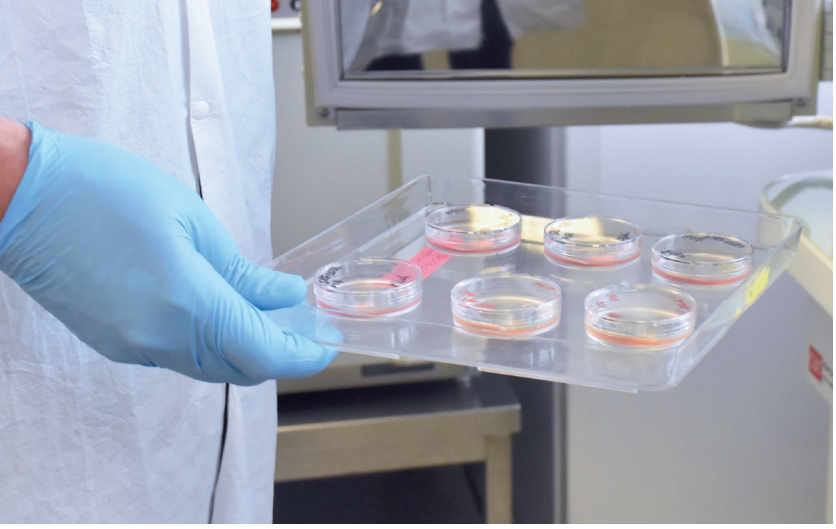
This study aims to identify new inflammation biomarkers in CA, whether in circulating blood, *in situ* or as imaging biomarkers, to better understand the pathophysiology of the disease and then determine the contribution to the clinical treatment and care of patients. The identification of new biomarkers, in particular circulating ones, would open up pathophysiological pathways which, in the long term, could lead to targeted treatments for autoimmune or inflammatory phenomena, in particular.



METABOLIC DISEASES OF THE LIVER

LITMUS (Liver Investigation: Testing Marker Utility in Steatohepatitis)
National Coordinator: **Prof. Vlad Ratziu**

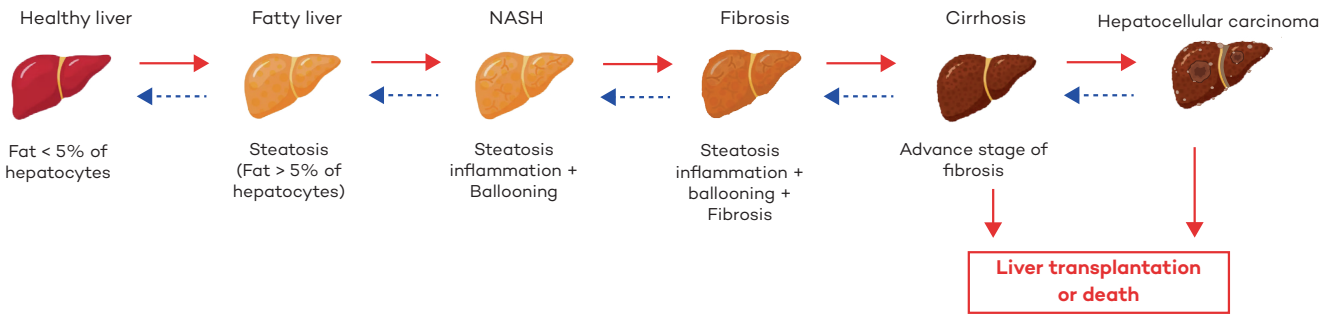
The LITMUS project, coordinated at the European level by Prof. Quentin Anstee at Newcastle University (United Kingdom) is a public-private consortium of more than 50 partners that aims to establish new biomarkers to predict the severity and rate of progression to the most severe forms of the disease, following on from the work carried out by the EpOS project. There is a significant paradox: a large proportion of the population has metabolic steatosis but only a minority progress to advanced liver disease or mortality. The transition of steatosis to steatohepatitis (Non-Alcoholic SteatoHepatitis) and then to fibrosis are important discriminating factors between a relatively benign prognosis and an increased risk of mortality. Liver biopsy remains the benchmark test despite its imperfect nature: it is complex and invasive and can involve sampling errors and a small but significant risk of complications. Such invasive examinations are not viable outside specialist practice and are particularly inappropriate for such a large "at risk" population. The lack of non-invasive and widely deployable biomarkers has impeded diagnosis, risk stratification and follow-up for many patients. This has also hampered the development of drugs and the conduct of clinical trials, which still rely on liver histology analysis as the evaluation criteria. The principal goal of LITMUS is to develop, robustly validate and obtain regulatory certification of new, innovative, non-invasive biomarkers to diagnose, stratify risk and monitor the progression of NAFLD/NASH and the fibrosis stage. Such biomarkers will help target care to those most at risk, and will ultimately facilitate the development of new drugs and treatments.



During the course of 2021, the IHU ICAN teams focused on collecting prospective samples and analysing the performance of various blood and imaging biomarkers, both from within the literature and our own cohort. We have already made the following significant advances:

- The LITMUS European register for metabolic steatosis and biocollection, which is the largest international register of patients with histologically-characterised metabolic steatosis
- Validation of the 7-level histological staging system - an important progress that will improve the granularity of patient assessment
- Meta-analyses of diagnostic accuracy studies that will provide insight into different biomarker threshold values to detect different target conditions in NAFLD
- Proof of principle that the metabolomic based on Magnetic resonance imaging (MRI) can be used to find non-invasive metabolic biomarkers to measure the onset and progression of NASH
- An atlas of histologic images that is available online for educational purposes, including training of general pathologists in the diagnosis of human NAFLD/NASH, the grading of necro-inflammatory activity, and the staging of fibrosis in liver biopsies
- Comparison of the NASH animal models

STAGES OF PROGRESSION FROM A HEALTHY LIVER TO A CARCINOMA



EU-PEARL (EU Patient-centric clinical trial platform)

National Coordinator: **Prof. Vlad Ratziu**

The EU-PEARL project aims to transform the current approach of therapeutic clinical trials focused on a single treatment into a platform trial approach, which can include several treatments from different companies and/or organisations simultaneously. To achieve this very ambitious goal, actors from the public and private sectors have formed a strategic alliance to develop a new Integrated Research Platform (IRP) paradigm for conducting these trials. This paradigm will focus on a master protocol that can accommodate multi-source treatments, while using the existing hospital infrastructure and federated patient data in the design, planning and execution of clinical trials. Additionally, this platform will aim to ensure an optimised regulatory pathway for the new treatments. Lastly, EU-PEARL will develop the infrastructure and tools that will pave the way for more efficient development of new treatments, all while improving the orientation of patients in therapeutic trials.

> **"THE EU-PEARL PROJECT AIMS TO TRANSFORM THE CURRENT APPROACH TO TREATMENT CLINICAL TRIALS."**
>
> Prof. Vlad Ratziu

There is a clinical need, for several diseases, for the faster development of new treatments. Currently, standard treatment clinical trials evaluate one drug at a time, which often involves sequential drug development cycles. In addition, from the patient's perspective, the current trial environment is at the root of cumbersome and delayed inclusion because of the timing imposed by sequential (not concurrent) evaluation in separate trials. Platform-based clinical trial design offers both a better chance of enrolling patients in a suitable trial, and more effective drug development opportunities that could subsequently accelerate the delivery of new treatments to patients. Although such multi-treatment platform trials are already underway for some neurological or oncological diseases, the lack of a general framework for this new clinical trial model creates a reluctance among stakeholders to initiate these collaborative approaches in a more systematic way. This became evident in the response to COVID-19: the only trials that could be completed in short timeframes were platform trials such as the RECOVERY trial. EU-PEARL aims to develop 4 ready-to-use IRP's based on 4 treatment areas: Major depressive disorder (MDD), Tuberculosis (TB), Non-alcoholic steatohepatitis (NASH) and neurofibromatosis (NF). Each of these fields has its own constraints, and the approach followed in these pathologies can serve as a model onto which other teams can build to initiate new IRP's in other fields.

Since the start of the project, the team has focused on implementing a common infrastructure for the creation of generic and disease-specific framework IRP's and drafting a NASH-specific protocol, while raising awareness among the partners and stakeholders of the benefits of adaptive platform trials. In addition to a communication and dissemination strategy, the EU-PEARL alliance is going to promote knowledge and understanding of the platform testing

methodology, and introduce the concept of an IRP, initiate collaborations with relevant external experts and initiatives to promote the future adoption of this innovative framework.
From a general perspective, guidelines on "data management and governance" have been developed. Further, to develop and share knowledge around platform trials among the partners, several documents have been made publicly accessible (available on the EU-PEARL website: https://eu-pearl.eu/).
In parallel, for NASH, the IHU-ICAN team conducted an inventory and assessment of the different existing clinical trial designs, and the specific challenges of drug development in NASH, in preparation for the design of the master protocol.

HOTSURFR (The Hepatic OuTcomes and SURvival Fatty liver Registry)

Coordinator: **Prof. Vlad Ratziu**

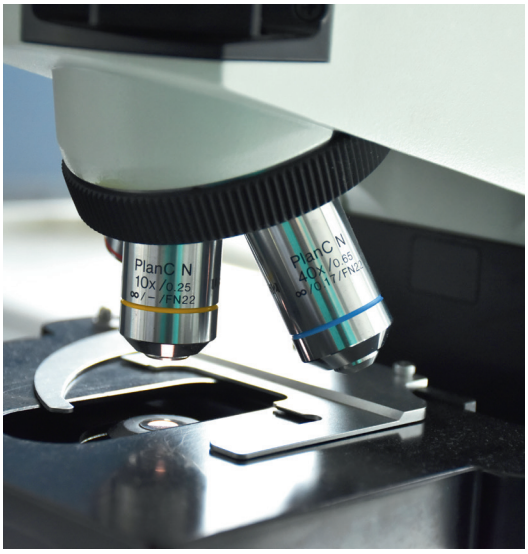
Late phase trials, including registration trials of new drugs for the treatment of NASH, are based on histological results of liver biopsies. As a consequence, understanding the prognostic significance of histological lesions and their classification is of utmost relevance. Unfortunately, the natural history of NASH is still poorly understood and, in particular, we lack clinical data on the prognostic significance of the elementary lesions of NASH, the categorisation of NAFLD pathological forms and the different stages of fibrosis.
A group of pathologists from the research consortia of the European FLIP and EPoS projects have recently proposed a new FLIP/SAF fibrosis staging classification, which finalises the new classification and resolves some of the drawbacks of the current fibrosis staging systems.

The goal of this registry is to implement a large retrospective cohort of international patients with histologically-confirmed NAFLD with long-term monitoring, in order to assess the predictive value of histological classification systems for mortality, hepato-carcinoma and end-stage liver diseases.

The study's goals are:

- To evaluate the prognostic value of a new EPoS NASH Fibrosis staging system, and SAF classification (Steatosis, Activity, Fibrosis).
- To provide estimates of disease progression in patients with mild NASH and progression to cirrhosis in non-cirrhotic NAFLD patients with serial biopsies.
- To understand the differences in outcomes between two cirrhotic NASH populations: those with florid steatohepatitis and those with burn-out cirrhosis.

At the end of 2021, 823 patients had been included in the study from 2 French centres (Pitié Salpêtrière the Angers University Hospital



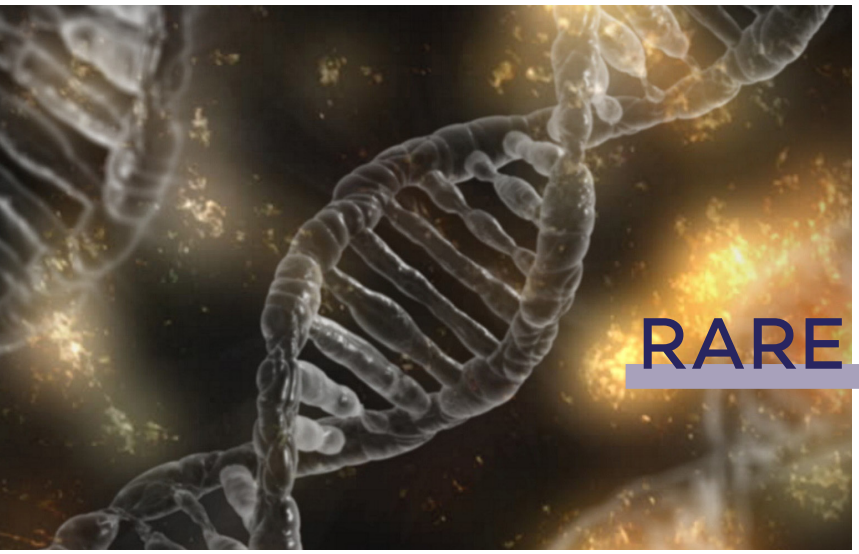
Centre), 2 Swedish centres, 1 Italian centre, 1 German centre and 1 Spanish centre. Statistical analyses are underway.

CORONASH

Coordinator: **Prof. Gérard Helft**

The relationship between metabolic steatosis of the liver (NAFLD), metabolic steatohepatitis of the liver (NASH) and atherosclerotic coronary artery disease (ACAD) is now recognised because of the common cardiometabolic risk factors (MRF's), the probable role of NAFLD/NASH in the onset of pre-atherosclerotic lesions and the myocardial dysfunction associated with NAFLD/NASH. We have previously shown that NAFLD is associated with the progression of carotid intima-media thickness and with the presence of diffuse atherosclerotic lesions (carotid, coronary and femoral). In prognostic terms, cardiovascular disease (CVD) is the leading cause of death in patients with NAFLD/NASH. For these reasons, The European Association For the Study of the Liver (EASL), recommends CVD testing in patients with NAFLD/NASH. By contrast, for patients with ACAD, the absence of recommendations on screening for NAFLD/NASH means the prevalence and severity of NAFLD/NASH are not known, and neither are the associations between the severity of liver disease and coronary heart disease, nor the profile of the highest-risk patients.
This is therefore an obstacle to the implementation of screening strategies, which are nonetheless necessary because both conditions are associated with their own mortality, even though they are treated by different medical specialties.

Our hypothesis is that NAFLD/NASH, possibly at an advanced fibrosis stage, is prevalent and increases with the severity of coronary lesions and thus, screening for advanced forms of NAFLD/NASH would be warranted in patients with ACAD. The hypothesis we propose at the pathogenic level to explain the possible influence of NAFLD/NASH on the severity of coronary damage takes into account several known mediators of atherosclerosis: trimethylamine-N-oxide (TMAO), advanced glycation end products (AGE's) and oxidised LDL. The main objective of the CORONASH study is to determine the prevalence of NAFLD/NASH in patients admitted to cardiology for suspected coronary disease.
At the end of 2021, 145 patients had been included in the study. Recruitment will continue until mid-October 2022.



RARE DISEASES

ID-STEM

Coordinator: **Prof. Irène Netchine, PU-PH, IFG System and foetal and post-natal growth**

Foetal and post-natal growth is finely regulated by genetic, epigenetic and environmental mechanisms. Parental imprinting is one regulation mechanism that allows monoallelic expression of certain genes from a single parental allele through differential methylation of the DNA. Imprinted genes play a very important role in the control of foetal and postnatal growth. These genes are grouped as 'clusters" in regions rich in CpG sites, DNA methylation sites, and are regulated by an Imprinting Center Region (ICR) and contain non-coding RNA. The 11p15 imprinted region is involved in Silver-Russell syndrome (SRS), a syndrome responsible for intrauterine and postnatal growth restriction. The principal molecular abnormalities identified in SRS are epigenetic modifications of the 11p15 region with hypomethylation at the H19/IGF2 locus, responsible for decreased IGF2 expression in the foetus. Although SRS is a rare cause of growth restriction, it provides a model for studying the pathophysiological mechanisms underlying foetal growth disorders in humans. The physiopathological mechanisms of these epimutations are largely unknown. Beckwith-Wiedemann Syndrome (BWS), the mirror opposite of SRS, is one cause of foetal macrosomia and 7.5 % of patients with BWS develop a tumour before the age of 5. BWS is also secondary to an alteration in the 11p15 imprinted region. The 14q32 region is also subject to parental imprinting and is implicated in Temple syndrome (TS), also a rare cause of fetal growth restriction.

Studying the consequences of these epimutations on the molecular signature of the imprinted gene network in these patients would provide a better understanding of the epigenetic mechanisms regulating foetal growth. As these genes are weakly expressed in fibroblasts, these studies will be conducted on pluripotent stem cells or IPSC's (Induced Pluripotent Stem Cells) obtained by reprogramming PBMC's from patients with SRS, BWS or TS. In a study of patients with Prader Willi syndrome with a deletion of the imprinting centre at the 15q11.2 locus (another region subject to imprinting), Stelzer's team demonstrated that the imprinting defects were maintained during reprogramming of human somatic cells into IPSC's.

We carry out the study in patients with epimutations of these regions and preferably with deletions or mutations of the 11p15 or

14q32 imprinting centres, in order to more reliably reproduce the epigenetic abnormalities during PBMC reprogramming.
The relevance of using blood mononuclear cells for reprogramming into induced pluripotency cells or iPS has already been demonstrated.

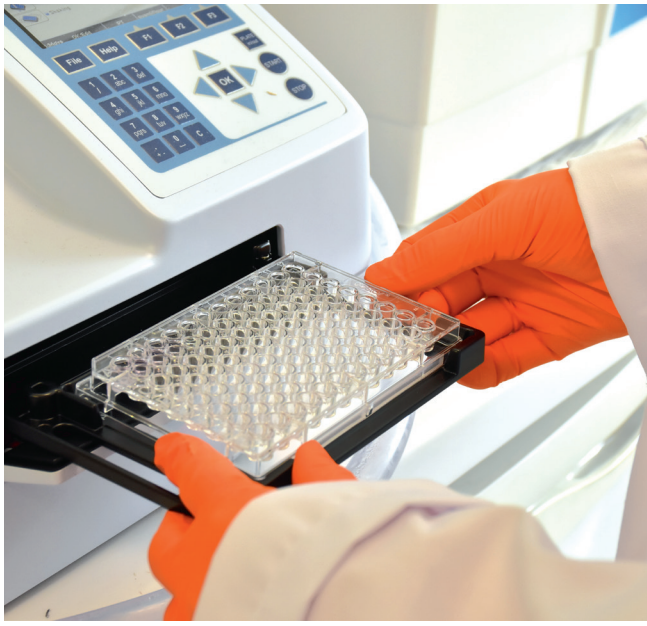
Reprogramming IPSC's from human somatic cells from SRS, BWS or TS patients would provide a model for studying the imprinted gene network. Because these cells are by definition pluripotent, IPSC's obtained from SRS, BWS or TS patients can then be re-differentiated into target cells for the study of foetal growth regulation (chondrocytes, adipocytes, neurons, hepatocytes).

DLK-1

Coordinator: **Prof. Irène Netchine**

Foetal growth restriction (FGR) predisposes to metabolic dysfunction later in life. Prenatal recognition of FGR is a challenge to enable proper monitoring and to improve foetal and neonatal outcomes. DLK1 is the product of an imprinted gene, located in humans on chromosome 14, expressed from the paternal allele during foetal development. Maternal uniparental disomy of chromosome 14 results in the absence of paternal expression of DLK1 and pre- and postnatal growth retardation. Mice lacking DLK1 have foetal and postnatal growth restriction, associated with a decrease in the growth hormone (GH). DLK1 is a transmembrane protein that can be split into a circulating form. Its concentration increases in the maternal circulation during pregnancy. It has recently been shown that the foetus is the source of maternal circulating DLK1 and that DLK1 levels in the third trimester are lower in the blood of women who will give birth to babies born small for their gestational age due to foetal growth restriction (FGR).

We are testing whether DLK1 can be used as a biomarker of FGR during the second trimester and will measure it at 24 weeks' gestation in the EDEN population-based prospective infant cohort study. Furthermore, in order to understand the role of DLK1 in growth regulation, we will study whether DLK1 is involved in the establishment of the somatotropic axis via the development of GHRH neurons in mouse models, in particular its expression in the hypothalamus during postnatal development. We will also test its potential role in axonal growth the and guidance of GHRH neuron development *in vitro* in cultured arcuate nuclei of GHRHeGFP mice, confirm its role *in vivo*, using transgenic mouse models with decreased DLK1, and lastly, study the link between DLK1 and nutrition in GHRH-eGFP mice that have a decreased somatotropic axis configuration due to early postnatal nutritional restriction.



Partnerships to accelerate innovation

Thanks to its integrated approach, the IHU ICAN creates favorable conditions to foster and help thrivepluri-disciplinary projects that connect academic research and industry private partners. Focus on 2 significant partnerships in 2021:

SCAI, Sorbonne Centre of Artificial Intelligence, is a transverse institute of Sorbonne University which federates teacher-researchers and researchers from the Faculty of Science and Engineering, the Faculty of Medicine and the Arts Faculty as well as the partners of the Sorbonne University Alliance (UTC, MNHN, Insead, CNRS, Inria, Inserm, CEA). Created in 2019 in a national and international context marked by intense competition in artificial intelligence, SCAI brings together a strategic range of modern artificial intelligence disciplines in a unique location in the heart of the Latin Quarter in Paris. SCAI aims to promote the development of interdisciplinary research projects focused on AI, in a dynamic and attractive environment. It also works with private partners (large groups, SME's, start-ups) through collaborative programmes. SCAI strongly supports methodological research at the heart of AI ("Mathematics, Computer Science, Robotics"), as well as more contextualised research via three priority themes: "Health and Medicine", "Climate, Environment, Universe" and "Digital Humanities". These themes represent scientific and societal challenges, and need the major impetus from the Sorbonne University Alliance to structure themselves and ensure proper data valorization. SCAI combines the AI research potential of all the Sorbonne University laboratories involved in health and medicine. To support MAESTRIA, the SCAI will in particular mobilise the research strengths of three laboratories involved in AI and medicine. Firstly, the Biomedical Imaging Laboratory (LIB - UMRS 1146), which specialises in fundamental and applied research on morphological, functional and molecular biomedical imaging methods for small animals and humans. Within MAESTRIA, the LIB will develop computer vision methods applied to the area of cardiac MRI. Secondly, the Institute of Intelligent Systems and Robotics (ISIR - UMR 7222), which is a multidisciplinary research laboratory bringing together researchers and academics from different engineering science disciplines. An important part of ISIR's activities is dedicated to medicine, imaging and life sciences. Research focuses on surgical and functional rehabilitation aids, micro/nanomanipulation in space and (biological) object characterisation techniques, haptic and tactile interfaces, and computer vision applied to medicine and health. MAESTRIA also requires the high level of expertise in mathematics and statistical models available within the Laboratory of Probabilities, Statistics et Modelling (LPSM) at Sorbonne University (LPSM - UMR 8001). Being the leading laboratory in France and one of the most important in the world, its scientific activities concern the modelling, description and estimation of random phenomena. Within MAESTRIA, the LPSM will brings its expertise to the development and validation of the statistical models necessary for the development of Machine Learning techniques.

MAESTRIA will thus have a major impact on the local scientific community, as it will enable the development of cutting-edge medical tools thanks to the grouping of health professionals and artificial intelligence experts around cardiac diagnosis.

MAESTRIA will enable the development

of models, concepts and tools that will naturally involve the project partners, who also have important AI assets. Indeed, Oxford (National Consortium of Intelligent Medical Imaging), Maastricht (Artificial Intelligence 4 Imaging) and Harvard (Department of Biomedical Informatics) are also home to world-class AI communities focused on imaging, health and medicine. The role of the SCAI will thus be to facilitate the joint development of methods and algorithms by drawing on all the network's strengths.
This effort, based on a broad collaboration including the EU, the UK and the US, will contribute naturally to increasing European innovation capacity in diagnostic tools, platforms and services.
SCAI is an important partner in MAESTRIA, a project that will thus have a lasting impact on inter-academic and international collaborations at the highest scientific level.

The mission of SCAI, the Artificial Intelligence Centre of Sorbonne University, is to federate the strengths in artificial intelligence (AI) of the Sorbonne University Alliance community, to encourage interdisciplinary collaborations and to facilitate access to the technologies for colleagues and students interested in the field.

ICAN has been a favoured partner of SCAI since the launch of the centre in 2019. Together we have identified many exciting issues around cardiology, diabetes, cutting-edge imaging and multimodal data fusion. In particular, our collaboration resulted in the very successful European MAESTRIA project on machine learning and artificial intelligence for the early detection of cerebral vascular accidents and atrial fibrillation. Another example is the ICONIC project, which aims to create a reference Atlas of 4D human cardiac imaging."

Gérard Biau - Professor,
Directeur, SCAI
Sorbonne University -
Laboratory of Probabilities,
Statistics and Modelling

metagenopolis mgps.eu

MetaGenoPolis-INRAE (MGP) and the IHU ICAN, synergy for accelerating microbiota and cardiovascular diseases in France.
Diabetes, obesity, cirrhosis, liver disease (NASH), Cardiovascular disease are chronic diseases that have increased steadily over the past fifty years, some of them in an uncontrolled way. They are the public health issues of today and tomorrow. These cardiometabolic diseases, affecting both children and adults, are the leading cause of death in France and worldwide. A more effective fight against these diseases will be achieved through innovative and multidisciplinary research that will enable us to offer personalised treatment and care to patients.
Science has shown that these diseases could be associated to imbalanced intestinal microbiota. We have to keep exploring the impact of microbiota on cardiovascular diseases to open up new treatment and care pathways.
MetaGenoPolis-INRAE and the IHU ICAN, both internationally recognised in the scientific community for their research work and part of the MetaGenoPolis pre-industrial demonstrator, wish to join forces to accelerate an understanding of the link between microbiota and cardiometabolic diseases.

MetaGenoPolis (MGP), an INRAE unit, is

an expert in intestinal microbiota research applied to human and animal health and nutrition to accelerate science and innovation. Funded by the Programme des Investissements d'Avenir (Programme for the Investments of the Future) Laureate 2012 and 2019, MGP has coordinated two significant projects that have advanced the science of microbiota: the MetaHIT project, which published the first catalogue of human intestinal microbial genes, and the IHMS project, which helps standardise the analysis of microbial DNA. MGP's scientific excellence in the analysis of intestinal microbiota and its implications for health and nutrition is widely recognised in the international scientific community. Since its creation in 2012, MetaGenoPolis has collaborated on 236 research projects, including 154 with industry partners.. MGP's primary missions are: to accelerate microbiota science in France and innovation in the field of health and food; to propose high-performance, high-throughput technologies for analysing the diversity of complex microbiota and the interactions between intestinal bacteria and human cells; to collaborate with manufacturing stakeholders in transforming their discoveries into health-related products and services, to identify and fully process leads for future industrial applications, and to help design and lead scientific projects towards applications.

Within the framework of TheFrench Gut project, a national contribution led by INRAE which will collect the intestinal microbiota of 100,000 adult volunteers residing in metropolitan France, as well as associated nutritional and clinical data by 2027, the INRAE/ICAN collaboration will enable the creation of synergies in ancillary projects to accelerate knowledge on the relationship between intestinal microbiota and cardiometabolic diseases in France. In fact, several patient cohorts under the aegis of the IHU could join Le French Gut in order to study this relationship.

Close links already exist between MetaGenoPolis-INRAE and ICAN, notably through two international projects, MetaHIT and Metacardis, which have resulted in high-impact publications, and more recently in joint discussions to propose offers to industry wishing to explore the microbiota and its impact on health.

Whether for diagnosis, treatment or prevention through nutrition, these partnership offers include the unique expertise of these two institutes (clinical, metagenomics and artificial intelligence) and benefit from high quality technical platforms to meet the increasingly innovative and personalised demands of our economic partners."

Alexandre Cavezza, PhD -
Director, MGP

Educating on Cardiometabolism

Sharing and distributing knowledge with the scientific and medical communities, and also with the general public, is an integral part of the IHU-ICAN's missions. Our understanding of cardiometabolic diseases and the how to treat themis evolving rapidly. Similarly, the constant changes in patient care pathways makes ever more dire the need to ensure wide dissemination of new healthcare expertise in order to improve patient treatment, care and quality of life.
As barriers between disciplines fall down and in lighe of the constant technological progress, the need to rethink the way we manage cardiometabolic and severe nutrition disorder patient pathways is all the more important.
The IHU ICAN is putting in place very practical tools to pass on to as many people as possible the innovations to which it contributes and is partnering with the best French engineering schools.

JUNIOR LIVING LAB

> SORBONNE POLYTECH

Since 2018 the IHU ICAN has been working with engineering students at Sorbonne POLYTECH as part of their second-year internship project. Their mission is to propose solutions to medical challenges encountered by clinicians within the IHU community 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. These projects are very stimulating for the students, who work on concrete devices that will one day change patients' lives.

An offloading shoe is in development
After a difficult 2019/2020 edition for the internees due to the health crisis, the class of 2020/2021 has given a serious boost to the project of a smart discharge shoe that discreetly signals to the patient that they are putting pressure on their chronic foot wound.. One of the suspected causes of these wounds is mechanical. Thus, the hypothesis formulated by Dr Georges Ha Van, an expert practitioner of diabetic foot, who works in Professor Hartemann's diabetology department, is that rigorous observance of pressure suppression promotes healing.

Two new prototypes have been developed and a manufacturer has shown interest in the idea. The work will continue into the pre-manufacturing phase.
In 2021 this project was supported by Entrepreneurs and Go.

> ÉCOLE CENTRALE D'ELECTRONIQUE

With our partner CAP GEMINI ENGINEERING, we have offered an internship to students of the ECE school. The challenge was to design a initial therapeutic education programme for patients with heart failure. The project provided a very enriching experience for the students and clinicians who supervised the developments and validated the medical aspects. Following the example of the footwear project, it will continue to move forward in 2022, with the arrival of new student displaying new skills.

Winter camp
Group 2021 postponed
to Spring 2022
due to the
health crisis

CMDO NETWORK WINTER CAMP

Since 2014, the traditional CMDO network winter camp has welcomed doctoral students/post-doctoral fellows and the young research staff of the IHU in Quebec. The pandemic did not allow for the 2021 edition to be held in person over the winter. Nevertheless, some of the training content was made available to the campers and a new cohort was formed in the spring of 2022.
The IHU ICAN took advantage of this COVID period to review its arrangements for hosting Canadian students and will launch its first summer camp in 2022!

MASTER Extra-Corporal Circulation and Circulatory Assistance M1

This Master was designed by Dr Aude Carillion and Prof. Guillance Lebreton, Institute of Cardiology, Pitié-Salpêtrière Hospital Group.
It will allow students to acquire:
• the fundamental and transversal bases necessary for the practice of extracorporeal circulation and circulatory assistance
• the fundamental bases for professional practice in an operating theatre, an intensive care unit and a hospital structure
• the epidemiological, ethical, legal, health economics and medical English bases.
Teams from the IHU ICAN participated in the design of that last module. Participation in this fully online format, born during COVID-19, opens great perspectives for developing training modules.

SORBONNE UNIVERSITÉ

Financial statement and social policy statement

SOCIAL

53
ICAN COLLABORATORS

68%
WOMEN

32%
MEN

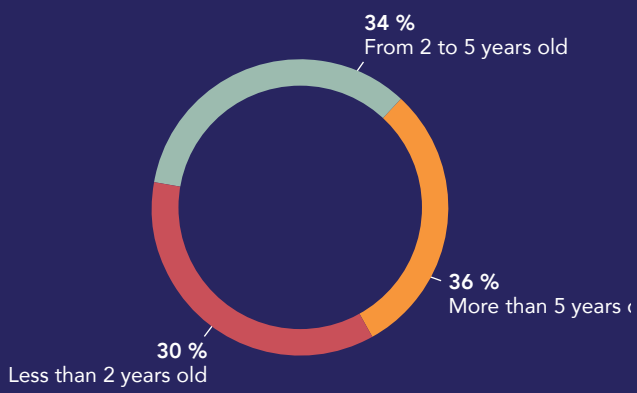
In 2021, the IHU ICAN employs about fifty collaborators working together on research projects in cardiometabolic and nutritional diseases.

The HR department is involved in supporting the teams, and has the following missions: supporting the managers, accompanying employees from recruitment to departure, recruiting and accompanying new employees, managing employees' administrative files, developing employees' skills, labour relations with the unions and staff representatives (despite the context, the 6 annual CSE's and 4 CSSCT's have been organised).

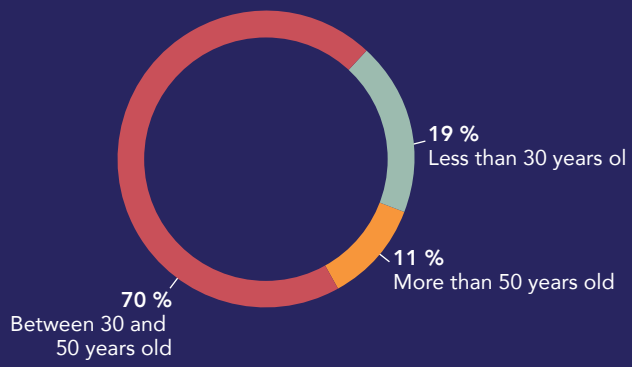
In 2021, the HR department participated in clarifying the occupational risks identified within the IHU, by finalising the update of the occupational risk assessment document (DUERP) and by regularly sending information and instructions to staff on the evolution of health regulations.

It was also mobilised to accompany the return to on-site activities while maintaining the dynamic of remote working. Thus, prior to the negotiations of the new remote working agreement (validated in October 2021), a survey was conducted in July 2021 among employees to assess their feelings regarding autonomy and efficiency in remote work, the quality and frequency of remote interactions with managers and colleagues and their degree of well-being while working remotely.

WORKFORCE BY **SENIORITY**



WORKFORCE BY **AGE**



POSITION **BREAKDOWN**

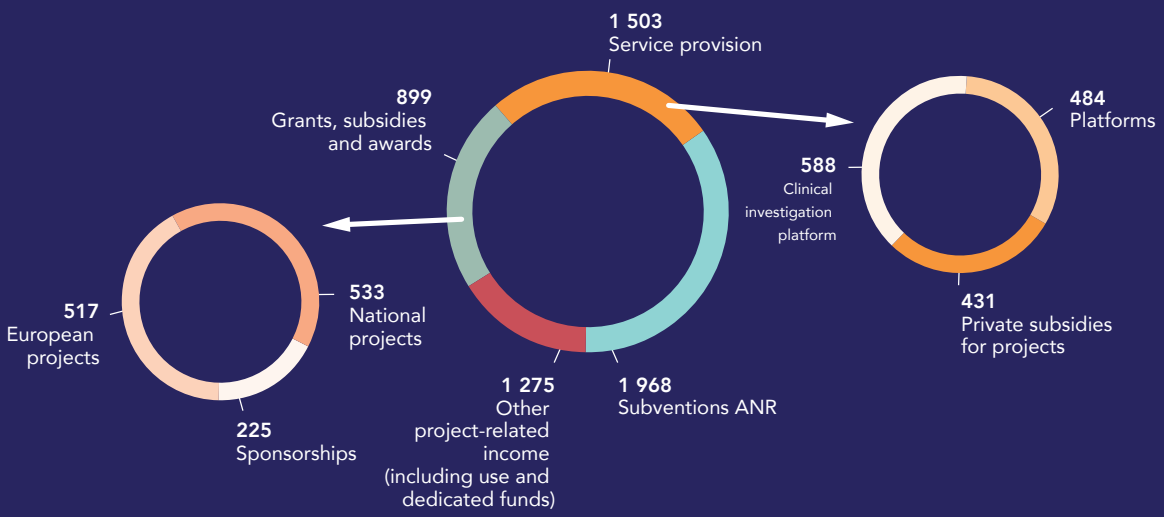
A DOZEN OR SO INTERNS WERE WELCOMED DURING 2021.

FINANCIAL

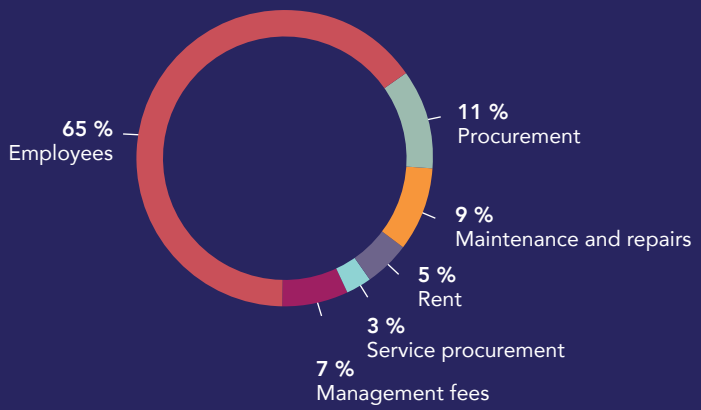
Faced with the challenge of defining an economic model aiming for financial autonomy more quickly than the other IHU's, an in-depth review was conducted of the core missions of the IHU. This helped identify a clear direction for the future: the ICAN must continue to refocus on its added value as a shared and fluid gateway for the scientific offerings of its community and its founders by the economic players. This is the context in which our financial management policy is evolving. European and international collaborations with the industry have been on the rise and the volume of services provided by ICAN's technological platforms is increasing.

INCOME STATEMENT IN €€		2021
Service and sales revenues		1,502,689
Grants, subsidies and awards		898,952
Other revenues (that use project dedicated funds)		1, 275, 551
of which Sponsorship		225,000
ANR grants		1, 967, 559
TOTAL OPERATING INCOME		**5, 644, 751**
Operating expenses		(1, 607, 012)
Depreciation and provision expenses		(564,218)
Employees		(2, 936, 911)
Project dedicated funds carried forward		(904,324)
TOTAL OPERATING EXPENSES		**(6, 012, 465)**
OPERATING PROFIT/LOSS		**(367,714)**
Financial profit/loss		3,780
	Financial income	3,780
	Financial expenses	-
Pre-tax profit/loss		(363,933)
	Exceptional income	204,245
	Exceptional expenses	(164,401)
Exceptional profit/loss		39,844
TOTALS		
TOTAL INCOME		**5, 852, 776**
TOTAL EXPENSES		**(6, 176, 866)**
NET PROFIT/LOSS		**(324,089)**

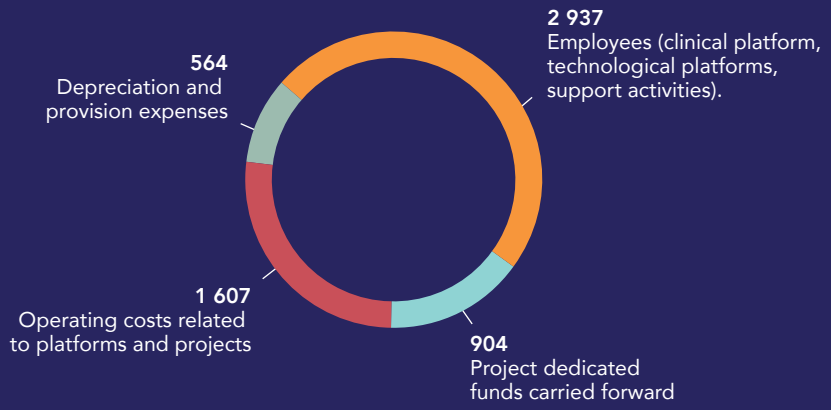
RESOURCES IN €K



USE OF THE ANR GRANT

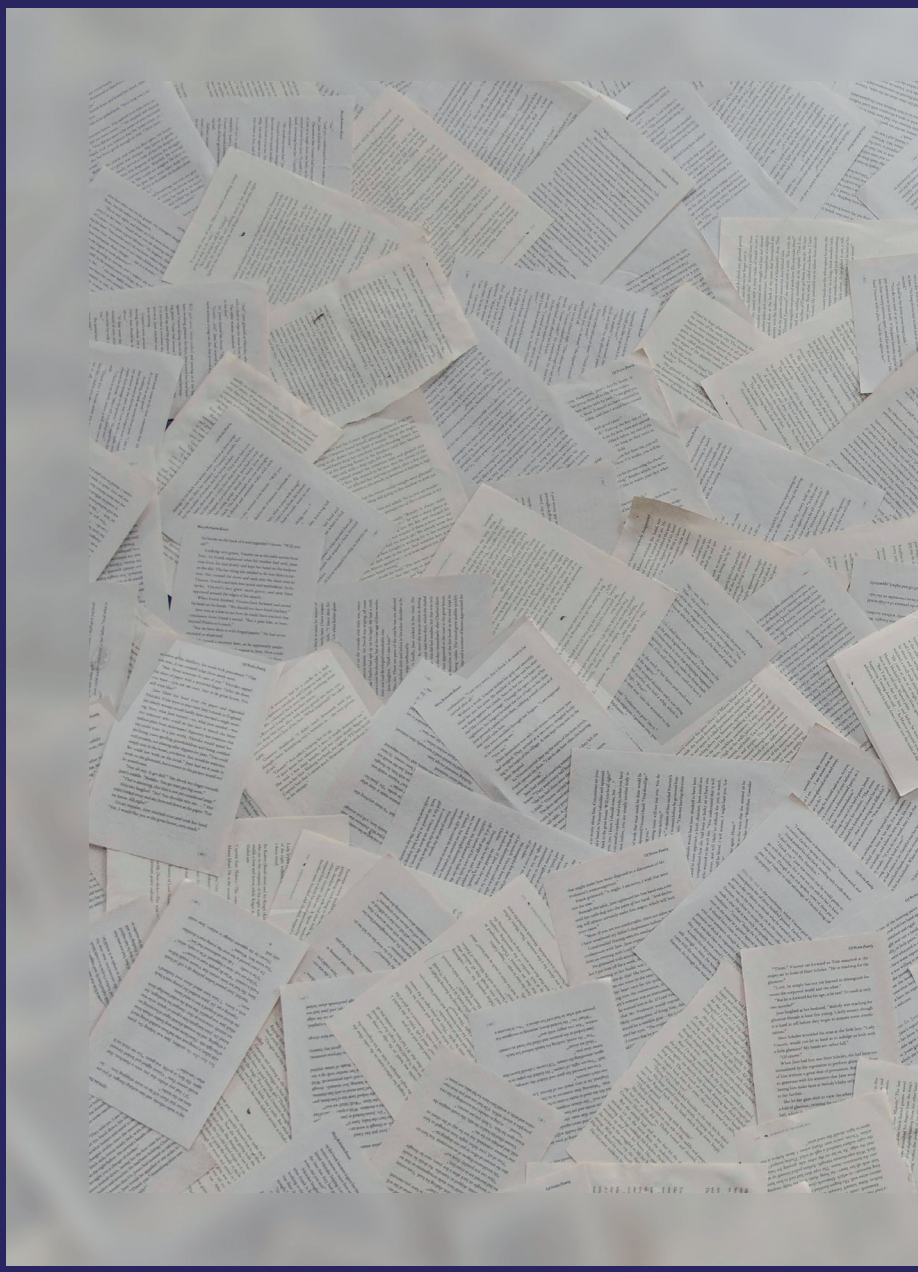


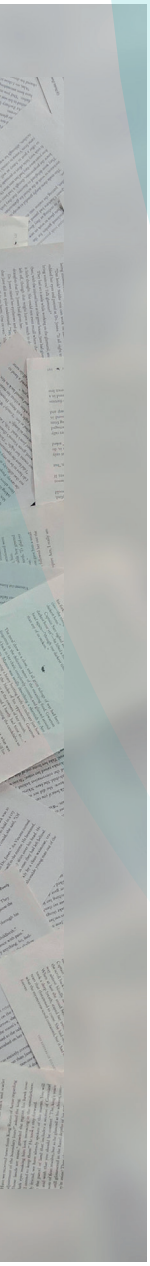
EXPENDITURES IN €K



2021 Publications

Non-exhaustive list





10 IMPACTFUL PUBLICATIONS FROM THE IHU ICAN COMMUNITY

1. Phan F, Boussouar S, Lucidarme O, Zarai M, Salem JE, Kachenoura N, Bouazizi K, Charpentier E, Niati Y, Bekkaoui H, Amoura Z, Mathian A, Benveniste O, Cacoub P, Allenbach Y, Saadoun D, Lacorte JM, Fourati S, Laroche S, Hartemann A, Bourron O, Andreelli F, Redheuil A; COVID-19 APHP.SU Group Cardiac adipose tissue volume and IL-6 level at admission are complementary predictors of severity and short-term mortality in COVID-19 diabetic patients **Cardiovasc Diabetol 2021 Aug 12**

2. Bouazizi K, Zarai M, Dietenbeck T, Aron-Wisnewsky J, Clément K, Redheuil A, Kachenoura N. Abdominal adipose tissue components quantification in MRI as a relevant biomarker of metabolic profile. **Magn Reson Imaging**. 2021 Jul

3. Forslund SK, Chakaroun R, Zimmermann-Kogadeeva M, Markó L, Aron-Wisnewsky J, ...; MetaCardis Consortium*, Gøtze JP, Køber L, Vestergaard H, Hansen T, Zucker JD, Hercberg S, Oppert JM, Letunic I, Nielsen J, Bäckhed F, Ehrlich SD, Dumas ME, Raes J, Pedersen O, Clément K, Stumvoll M, Bork P. Combinatorial, additive and dose-dependent drug-microbiome associations. **Nature**. 2021 Dec;

4. Lécuyer E, Le Roy T, Gestin A, Lacombe A, Philippe C, Ponnaiah M, Huré JB, Fradet M, Ichou F, Boudebbouze S, Huby T, Gautier E, Rhimi M, Maguin E, Kapel N, Gérard P, Venteclef N, Garlatti M, Chassaing B, Lesnik P. Tolerogenic Dendritic Cells Shape a Transmissible Gut Microbiota That Protects From Metabolic Diseases. **Diabetes**. 2021 Sep

5. Ma F, Darabi M, Lhomme M, Tubeuf E, Canicio A, Brerault J, Medadje N, Rached F, Lebreton S, Frisdal E, Brites F, Serrano C, Santos R, Gautier E, Huby T, El Khoury P, Carrié A, Abifadel M, Bruckert E, Guerin M, Couvert P, Giral P, Lesnik P, Le Goff W, Guillas I, Kontush A. Phospholipid transfer to high-density lipoprotein (HDL) upon triglyceride lipolysis is directly correlated with HDL-cholesterol levels and is not associated with cardiovascular risk.**Atherosclerosis**. 2021 May

6. Gizon M, Duboscq-Bidot L, El Kassar L, Bobin P, Ader F, Giraud-Triboult K, Charron P, Villard E, Fontaine V, Neyroud N. Generation of a heterozygous SCN5A knockout human induced pluripotent stem cell line by CRISPR/Cas9 edition.**Stem Cell Res**. 2022 Apr

7. Suffee N, Baptista E, Piquereau J, Ponnaiah M, Doisne N, Ichou F, Lhomme M, Pichard C, Galand V, Mougenot N, Dilanian G, Lucats L, Balse E, Mericskay M, Le Goff W, Hatem SN. Impacts of a high fat diet on the metabolic profile and the phenotype of atrial myocardium in mice.**Cardiovasc Res**. 2021 Dec 31

8. Hékimian G, Kerneis M, Zeitouni M, Cohen-Aubart F, Chommeloux J, Bréchot N, Mathian A, Lebreton G, Schmidt M, Hié M, Silvain J, Pineton de Chambrun M, Haroche J, Burrel S, Marot S, Luyt CE, Leprince P, Amoura Z, Montalescot G, Redheuil A, Combes A. Coronavirus Disease 2019 Acute Myocarditis and Multisystem Inflammatory Syndrome in Adult Intensive and Cardiac Care Units **Chest**. 2021 Feb

9. Ratziu V, de Guevara L, Safadi R, Poordad F, Fuster F, Flores-Figueroa J, Arrese M, Fracanzani AL, Ben Bashat D, Lackner K, Gorfine T, Kadosh S, Oren R, Halperin M, Hayardeny L, Loomba R, Friedman S; ARREST investigator study group, Sanyal AJ. Aramchol in patients with nonalcoholic steatohepatitis: a randomized, double-blind, placebo-controlled phase 2b trial.**Nat Med**. 2021 Oct 27;

10. Garnier S, Harakalova M, Weiss S, Mokry M, Regitz-Zagrosek V, Hengstenberg C, Cappola TP, Isnard R, Arbustini E, Cook SA, van Setten J, Calis JJA, Hakonarson H, Morley MP, Stark K, Prasad SK, Li J, O'Regan DP, ..., Besse C, Fontaine V, Blanché H, Ader F, Keating B, Curjol A, Boland A, Komajda M, Cambien F, Deleuze JF, Dörr M, Asselbergs FW, Villard E, Trégouët DA, Charron P. Genome-wide association analysis in dilated cardiomyopathy reveals two new players in systolic heart failure on chromosomes 3p25.1 and 22q11.23 **Eur Heart J**. 2021 May 21.

LIST OF ARTICLES WITH A HIGHEST SIGAPS SCORE

(published in high-level journals by medical/scientific discipline, with authors from the IHU ICAN community - first, second or correspondent - Non-exhaustive list)

1. Amarenco P, Kim JS, Labreuche J, Charles H, Giroud M, Lavallée PC, Lee BC, Mahagne MH, Meseguer E, Nighoghossian N, Steg PG, Vicaut É, Bruckert E - Intracranial Hemorrhage in the TST Trial. – **Stroke** - 2021 Dec 29.

2. Luyt CE, Hajage D, Burrel S, Hraiech S, Diallo MH, Papazian L, Boutolleau D - Efficacy of Acyclovir to Suppress Herpes Simplex Virus Oropharyngeal Reactivation in Patients Who Are Mechanically Ventilated: An Ancillary Study of the Preemptive Treatment for Herpesviridae (PTH) Trial. - **JAMA Netw Open** - 2021 Dec 1

3. Lim C, Turco C, Balci D, Savier E, Goumard C, Perdigao F, Rousseau G, Soubrane O, Scatton O - Auxiliary Liver Transplantation for Cirrhosis: From APOLT to RAPID: A Scoping Review. - **Ann Surg** -2022 Mar 1

4. Hatem SN, Cohen A - Atrial fibrillation and stroke: are we looking in the right direction? - **Cardiovasc Res** - 2022 Jan 7

5. Pineton de Chambrun M, Moyon Q, Faguer S, Urbanski G, Mathian A, Zucman N, Werner M, Luyt CE, Verlicchi F, Amoura Z - The Consequences Of COVID-19 Pandemic On Patients With Monoclonal Gammopathy Associated Systemic Capillary-Leak Syndrome (Clarkson's disease) - **J Allergy Clin Immunol Pract** - february 01, 2022

6. Freund Y, Chauvin A, Jimenez S, Philippon AL, Curac S, Fémy F, Gorlicki J, Chouihed T, Goulet H, Montassier E, Dumont M, Lozano Polo L, Le Borgne P, Khellaf M, Bouzid D, Raynal PA, Abdessaied N, Laribi S, Guenezan J, Ganansia O, Bloom B, Miró O, Cachanado M, Simon T - Effect of a Diagnostic Strategy Using an Elevated and Age-Adjusted D-Dimer Threshold on Thromboembolic Events in Emergency Department Patients With Suspected Pulmonary Embolism: A Randomized Clinical Trial. – **JAMA** - 2021 Dec 7

7. Silvain J, Hausenloy D, Zeitouni M - Appropriate criteria for the definition of Type 4a MI. - **Eur Heart J** - 2021 Mar 3

8. Zeitouni M, Collet JP - Pretreatment in the Setting of Non-ST-Elevated Acute Coronary Syndrome-When It Is Time to Change. - **JAMA Netw Open** - 2021 Nov 1

9. Rinella M, Dufour JF, Anstee QM, Goodman Z, Younossi Z, Harrison SA, Loomba R, Sanyal AJ, Bonacci M, Trylesinski A, Natha M, Shringarpure R, Granston T, Venugopal A, Ratziu V - Non-invasive evaluation of response to obeticholic acid in patients with NASH: Results from the REGENERATE study. - **J Hepatol** - 2022 Mar

10. Marcelin G, Gautier EL, Clément K - Adipose Tissue Fibrosis in Obesity: Etiology and Challenges. - **Annu Rev Physiol** -2022 Feb 10

11. Ratziu V, Rinella ME, Neuschwander-Tetri BA, Lawitz E, Denham D, Kayali Z, Sheikh A, Kowdley KV, Desta T, Elkhashab M, DeGrauw J, Goodwin B, Ahmad A, Adda N - EDP-305 in patients with NASH: A phase II double-blind placebo-controlled dose-ranging study. - **J Hepatol** - 2022 Mar

12. Motovska Z, Montalescot G - The Cornelian dilemma† of quitting DAPT. - **Eur Heart J** - 2021 Dec 1

13. Savier E, Simon-Gracia L, Charlotte F, Tuffery P, Teesalu T, Scatton O, Rebollo A - Bi-Functional Peptides as a New Therapeutic Tool for Hepatocellular Carcinoma. – **Pharmaceutics** - 2021 Oct 6

14. Aubart FC, Poupel L, Saint-Charles F, Charlotte F, Arsafi Y, Frisdal E, Roos-Weil D, Emile JF, Amoura Z, Guerin M, Lesnik P, Haroche J, Le Goff W - Profound systemic alteration of the immune phenotype and an immunoglobulin switch in Erdheim-Chester disease in a single-center of 78 patients. – **Haematologica** - 2021 Jun 1

15. Freund Y, Roussel M, Behringer W - Safety of the 4PEPS in Patients With a Very Low Prevalence of Pulmonary Embolism-Need for More Than a Point Estimate. - **JAMA Cardiol** - 2021 Dec 1

16. Logeart D, Berthelot E, Bihry N, Eschalier R, Salvat M, Garcon P, Eicher JC, Cohen A, Tartiere JM, Samadi A, Donal E, DeGroote P, Mewton N, Mansencal N, Raphael P, Ghanem N, Seronde MF, Chavelas C, Rosamel Y, Beauvais F, Kevorkian JP, Diallo A, Vicaut E, Isnard R - Early and short-term intensive management after discharge for patients hospitalized with acute heart failure, a randomized study (ECAD-HF). - **Eur J Heart Fail** - 2021 Oct 21

17. Ratziu V, de Guevara L, Safadi R, Poordad F, Fuster F, Flores-Figueroa J, Arrese M, Fracanzani AL, Ben Bashat D, Lackner K, Gorfine T, Kadosh S, Oren R, Halperin M, Hayardeny L, Loomba R, Friedman S, Sanyal AJ - Aramchol in patients with nonalcoholic steatohepatitis: a randomized, double-blind, placebo-controlled phase 2b trial. -**Nat Med** - 2021 Oct 7

18. Moyon Q, Sterlin D, Miyara M, Anna F, Mathian A, Lhote R, Ghillani-Dalbin P, Breillat P, Mudumba S, de Alba S, Cohen-Aubart F, Haroche J, Pha M, Boutin THD, Chaieb H, Flores PM, Charneau P, Gorochov G, Amoura Z - BNT162b2 vaccine-induced humoral and cellular responses against SARS-CoV-2 variants in systemic lupus erythematosus. - **Ann Rheum Dis** - 2022 Apr

19. Cusi K, Alkhouri N, Harrison SA, Fouqueray P, Moller DE, Hallakou-Bozec S, Bolze S, Grouin JM, Jeannin Megnien S, Dubourg J, Ratziu V - Efficacy and safety of PXL770, a direct AMP kinase activator, for the treatment of non-alcoholic fatty liver disease (STAMP-NAFLD): a randomised, double-blind, placebo-controlled, phase 2a study. - **Lancet Gastroenterol Hepatol** - 2021 Sep 22

20. Capeau J - Weight and antiretrovirals: a new episode in a long series. - **Lancet HIV** - 2021 Nov

21. Le Pelletier L, Mantecon M, Gorwood J, Auclair M, Foresti R, Motterlini R, Laforge M, Atlan M, Fève B, Capeau J, Lagathu C, Bereziat V - Metformin alleviates stress-induced cellular senescence of aging human adipose stromal cells and the ensuing adipocyte dysfunction. – **Elife** - 2021 Sep 21

22. Faucher P, Beuvon F, Fignani D, Sebastiani G, Afonso G, Zhou Z, Dousset B, Boitard C, Dotta F, Mallone R, Larger E - Immunoregulated insulitis and slow-progressing type 1 diabetes after duodenopancreatectomy. – **Diabetologia** - 2021 Dec

23. Prifti E, Fall A, Davogustto G, Pulini A, Denjoy I, Funck-Brentano C, Khan Y, Durand-Salmon A, Badilini F, Wells QS, Leenhardt A, Zucker JD, Roden DM, Extramiana F, Salem JE - Deep learning analysis of electrocardiogram for risk prediction of drug-induced arrhythmias and diagnosis of long QT syndrome. - **Eur Heart J** - 2021 Oct 7

24. Nielsen MJ, Leeming DJ, Goodman Z, Friedman S, Frederiksen P, Rasmussen DK, Vig P, Seyedkazemi S, Fischer L, Torstenson R, Karsdal MA, Lefebvre E, Sanyal AJ, Ratziu V - Comparison of ADAPT, FIB4 and APRI as non-invasive predictors of liver fibrosis and NASH within the CENTAUR Screening Population. - **J Hepatol** - 2021 Dec

25. Savier E, de Rycke Y, Lim C, Goumard C, Rousseau G, Perdigao F, Rufat P, Salloum C, Llado L, Ramos E, Lopez-Dominguez J, Cachero A, Fabregat J, Azoulay D, Scatton O - Novel Composite Endpoint for Assessing Outcome in Liver Transplantation: Arterial and Biliary Complication-Free Survival. - **Liver Transpl** - 2022 Jan

26. Poynard T, Paradis V, Mullaert J, Deckmyn O, Gault N, Marcault E, Manchon P, Si Mohammed N, Parfait B, Ibberson M, Gautier JF, Boitard C, Czernichow S, Larger E, Drane F, Castille JM, Peta V, Brzustowski A, Terris B, Vallet-Pichard A, Roulot D, Laouénan C, Bedossa P, Castera L, Pol S, Valla D - Prospective external validation of a new non-invasive test for the diagnosis of non-alcoholic steatohepatitis in patients with type 2 diabetes. - **Aliment Pharmacol Ther** - 2021 Oct

27. Levy D, Lebreton G, Pineton de Chambrun M, Hékimian G, Chommeloux J, Bréchot N, Luyt CE, Leprince P, Combes A, Schmidt M - Outcomes of Patients Denied ECMO During the COVID-19 Pandemic in Greater Paris, France. - **Am J Respir Crit Care Med** - 2021 Oct 15

28. Salem JE, Nguyen LS, Moslehi JJ, Ederhy S, Lebrun-Vignes B, Roden DM, Funck-Brentano C, Gougis P - Anticancer drug-induced life-threatening ventricular arrhythmias: a World Health Organization pharmacovigilance study. - **Eur Heart J** - 2021 Oct 7

29. Gautheron J, Morisseau C, Chung WK, Zammouri J, Auclair M, Baujat G, Capel E, Moulin C, Wang Y, Yang J, Hammock BD, Cerame B, Phan F, Fève B, Vigouroux C, Andreelli F, Jeru I - EPHX1 mutations cause a lipoatrophic diabetes syndrome due to impaired epoxide hydrolysis and increased cellular senescence. – **Elife** - 2021 Aug 3

30. Lobe C, Vallette M, Arbelaiz A, Gonzalez-Sanchez E, Izquierdo L, Pellat A, Guedj N, Louis C, Paradis V, Banales JM, Coulouarn C, Housset C, Vaquero J, Fouassier L - ZEB1 promotes cholangiocarcinoma progression through tumor dedifferentiation and tumor-stroma paracrine signaling. – **Hepatology** - 2021 Dec

31. Gallo A, Pérez de Isla L, Charrière S, Vimont A, Alonso R, Muñiz-Grijalvo O, Díaz-Díaz JL, Zambón D, Moulin P, Bruckert E, Mata P, Béliard S - The Added Value of Coronary Calcium Score in Predicting Cardiovascular Events in Familial Hypercholesterolemia. - **JACC Cardiovasc Imaging** - 2021 Dec

32. Mazzola A, Todesco E, Drouin S, Hazan F, Marot S, Thabut D, Varnous S, Soulié C, Barrou B, Marcelin AG, Conti F - Poor Antibody Response after Two Doses of SARS-CoV-2 vaccine in Transplant Recipients. - **Clin Infect Dis** - 2021 Mar 23

33. Chaumont C, Suffee N, Gandjbakhch E, Balse E, Anselme F, Hatem SN - Epicardial origin of cardiac arrhythmias: clinical evidences and pathophysiology. - **Cardiovasc Res** - 2021 Jun 22

34. Kerneis M, Montalescot G - RAS inhibition and COVID-19: more questions than answers? - **Lancet Respir Med** - 2021 Aug

35. Collet JP, Thiele H, Giannitsis E, Sibbing D, Barthélémy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Jüni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Siontis GCM, Barbato E, Hamm CW, Böhm M, Cornel JH, Ferreiro JL, Frey N, Huber K, Kubica J, Navarese EP, Mehran R, Morais J, Storey RF, Valgimigli M, Vranckx P, James S, Crea F - Debate: Prasugrel rather than ticagrelor is the preferred treatment for NSTE-ACS patients who proceed to PCI and pretreatment should not be performed in patients planned for an early invasive strategy. - **Eur Heart J** - 2021 Aug 17

36. Bellicha A, van Baak MA, Battista F, Beaulieu K, Blundell JE, Busetto L, Carraça EV, Dicker D, Encantado J, Ermolao A, Farpour-Lambert N, Pramono A, Woodward E, Oppert JM - Effect of exercise training before and after bariatric surgery: A systematic review and meta-analysis. - **Obes Rev** - 2021 Jul

37. Oppert JM, Bellicha A, van Baak MA, Battista F, Beaulieu K, Blundell JE, Carraca EV, Encantado J, Ermolao A, Pramono A, Farpour-Lambert N, Woodward E, Dicker D, Busetto L - Exercise training in the management of overweight and obesity in adults: Synthesis of the evidence and recommendations from the European Association for the Study of Obesity Physical Activity Working Group - **Obes. Rev.**- 2021 Ju

38. Chosidow O, Bernigaud C, Guillemot D, Giraudeau B, Lespine A, Changeux JP, Bourhy H, Lecuit M, Amoura Z - Ivermectin as a potential treatment for COVID-19? - **PLoS Negl Trop Dis** - 2021 Jun 1

39. Dolladille C, Ederhy S, Ezine E, Choquet S, Nguyen LS, Alexandre J, Moslehi JJ, Dechartres A, Salem JE - Chimeric Antigen Receptor T-Cells Safety: A pharmacovigilance & meta-analysis study. - **Am J Hematol** - 2021 Sep 1

40. Soulat-Dufour L, Fauvel C, Weizman O, Barbe T, Pezel T, Mika D, Cellier J, Geneste L, Panagides V, Marsou W, Deney A, Attou S, Delmotte T, Ribeyrolles S, Chemaly P, Karsenty C, Giordano G, Gautier A, Duceau B, Sutter W, Chaumont C, Guilleminot P, Sagnard A, Pastier J, Trimaille A, Bonnet G, Canu M, Coisne A, Cohen A - Prognostic value of right ventricular dilatation in patients with COVID-19: a multicentre study. - **Eur Heart J Cardiovasc Imaging** - 2022 Mar 22

41. Cohen Aubart F, Idbaih A, Emile JF, Amoura Z, Abdel-Wahab O, Durham BH, Haroche J, Diamond EL - Histiocytosis and the nervous system: from diagnosis to targeted therapies. - **Neuro Oncol** - 2021 Sep 1

42. Amarenco P, Kim JS, Labreuche J, Charles H, Giroud M, Lee BC, Lavallée PC, Mahagne MH, Meseguer E, Nighoghossian N, Steg PG, Vicaut E, Bruckert E - Impact of lower vs higher LDL cholesterol targets on cardiovascular events after ischemic stroke in diabetic patients. – **Diabetes** - 2021 Aug

43. Battista F, Ermolao A, van Baak MA, Beaulieu K, Blundell JE, Busetto L, Carraça EV, Encantado J, Dicker D, Farpour-Lambert N, Pramono A, Bellicha A, Oppert JM - Effect of exercise on cardiometabolic health of adults with overweight or obesity: Focus on blood pressure, insulin resistance, and intrahepatic fat-A systematic review and meta-analysis. - **Obes Rev** - 2021 Jul

44. Carraça EV, Encantado J, Battista F, Beaulieu K, Blundell JE, Busetto L, van Baak M, Dicker D, Ermolao A, Farpour-Lambert N, Pramono A, Woodward E, Bellicha A, Oppert JM - Effect of exercise training on psychological outcomes in adults with overweight or obesity: A systematic review and meta-analysis. - **Obes Rev** - 2021 Jul

45. Carraça EV, Encantado J, Battista F, Beaulieu K, Blundell JE, Busetto L, van Baak M, Dicker D, Ermolao A, Farpour-Lambert N, Pramono A, Woodward E, Bellicha A, Oppert JM - Effect of exercise training on psychological outcomes in adults with overweight or obesity: An overview of 12 systematic reviews and 149 studies. - **Obes Rev** - 2021 Jul

46. Carraça E, Encantado J, Battista F, Beaulieu K, Blundell J, Busetto L, van Baak M, Dicker D, Ermolao A, Farpour-Lambert N, Pramono A, Woodward E, Bellicha A, Oppert JM - Effective behavior change techniques to promote physical activity in adults with overweight or obesity: A systematic review and meta-analysis. - **Obes Rev** - 2021 Jul

47. Beaulieu K, Blundell JE, van Baak MA, Battista F, Busetto L, Carraça EV, Dicker D, Encantado J, Ermolao A, Farpour-Lambert N, Pramono A, Woodward E, Bellicha A, Oppert JM - Effect of exercise training interventions on energy intake and appetite control in adults with overweight or obesity: A systematic review and meta-analysis. - **Obes Rev** - 2021 Jul

48. van Baak MA, Pramono A, Battista F, Beaulieu K, Blundell JE, Busetto L, Carraça EV, Dicker D, Encantado J, Ermolao A, Farpour-Lambert N, Woodward E, Bellicha A, Oppert JM - Effect of different types of regular exercise on physical fitness in adults with overweight or obesity: Systematic review and meta-analyses. - **Obes Rev** - 2021 Jul

49. Schmidt M, Pineton de Chambrun M, Lebreton G, Hékimian G, Chommeloux J, Bréchot N, Barhoum P, Lefevre L, Juvin C, Molle J, Luyt CE, Combes A - Extracorporeal Membrane Oxygenation Instead of Invasive Mechanical Ventilation in a Patient with Severe COVID-19-associated Acute Respiratory Distress Syndrome. - **Am J Respir Crit Care Med** - 2021 Jun 15

50. Pineton de Chambrun M, Brodie D, Combes A - Appraising the Real-Life Need for ECMO During the COVID-19 Pandemic. - **Am J Respir Crit Care Med** - 2021 Jul 1

51. Lebreton G, Schmidt M, Ponnaiah M, Folliguet T, Para M, Guihaire J, Lansac E, Sage E, Cholley B, Mégarbane B, Cronier P, Zarka J, Da Silva D, Besset S, Lacombat I, Mongardon N, Richard C, Duranteau J, Cerf C, Saiydoun G, Sonneville R, Chiche JD, Nataf P, Longrois D, Combes A, Leprince P - Extracorporeal membrane oxygenation network organisation and clinical outcomes during the COVID-19 pandemic in Greater Paris, France: a multicentre cohort study. - **Lancet Respir Med** - 2021 Aug

52. Tanaka A, Hirohara J, Nakano T, Matsumoto K, Chazouillères O, Takikawa H, Hansen BE, Carrat F, Corpechot C - Association of bezafibrate with transplant-free survival in patients with primary biliary cholangitis. - **J Hepatol** - 2021 Sep

53. Hatem SN - Revealing the molecular history of the transition from paroxysmal to permanent atrial fibrillation. - **Cardiovasc Res** - 2021 Jun 16

54. Capeau J - Ageing with HIV: is the virus or the treatment guilty? - **Lancet HIV** - 2021 Apr

55. Hobeika C, Cauchy F, Fuks D, Barbier L, Fabre JM, Boleslawski E, Regimbeau JM, Farges O, Pruvot FR, Pessaux P, Salamé E, Soubrane O, Vibert E, Scatton O - Laparoscopic versus open resection of intrahepatic cholangiocarcinoma: nationwide analysis. - **Br J Surg** - 2021 Apr 30

56. Soret PA, Lam L, Carrat F, Smets L, Berg T, Carbone M, Invernizzi P, Leroy V, Trivedi P, Cazzagon N, Weiler-Normann C, Alric L, Rosa-Hezode I, Heurgué A, Cervoni JP, Dumortier J, Potier P, Roux O, Silvain C, Bureau C, Anty R, Larrey D, Levy C, Pares A, Schramm C, Nevens F, Chazouillères O, Corpechot C - Combination of fibrates with obeticholic acid is able to normalise biochemical liver tests in patients with difficult-to-treat primary biliary cholangitis. - **Aliment Pharmacol Ther** - 2021 May

57. Lebreton G, Dorgham K, Quentric P, Combes A, Gorochov G, Schmidt M - Longitudinal Cytokine Profiling in Severe COVID-19 Patients on ECMO and Haemoadsorption. - **Am J Respir Crit Care Med** - 2021 Jun 1

58. Barthélémy O, Rouanet S, Brugier D, Vignolles N, Bertin B, Zeitouni M, Guedeney P, Hauguel-Moreau M, Hage G, Overtchouk P, Akin I, Desch S, Vicaut E, Zeymer U, Thiele H, Montalescot G - Predictive Value of the Residual SYNTAX Score in Patients With Cardiogenic Shock. - **J Am Coll Cardiol** - 2021 Jan 19

59. Cohen Aubart F, Roos-Weil D, Armand M, Marceau-Renaut A, Emile JF, Duployez N, Charlotte F, Poulain S, Lhote R, Hélias-Rodzewicz Z, Della-Valle V, Bernard O, Maloum K, Nguyen-Khac F, Donadieu J, Amoura Z, Abdel-Wahab O, Haroche J - High frequency of clonal hematopoiesis in Erdheim-Chester disease. – **Blood** - 2021 Jan 28

60. Charreire H, Roda C, Feuillet T, Piombini A, Bardos H, Rutter H, Compernolle S, Mackenbach JD, Lakerveld J, Oppert JM - Walking, cycling, and public transport for commuting and non-commuting travels across 5 European urban regions: Modal choice correlates and motivations - **J. Transp. Geogr.** – 2021 Mar

61. Weill A, Demeret S, Ingen-Housz-Oro S, Colin A, Bagate F, de Prost N, Weiss N - Axonal Guillain-Barré syndrome and toxic epidermal necrolysis: two cases. - **J Eur Acad Dermatol Venereol** - J Eur Acad Dermatol Venereol - 2022 May

62. Savier E, Lim C, Scatton O - Liver transplant from controlled donation after circulatory death donors with normothermic regional perfusion versus donation after drain death donors. - **Liver Transpl** - 2021 Mar

63. Power JR, Alexandre J, Choudhary A, Ozbay B, Hayek S, Asnani A, Tamura Y, Aras M, Cautela J, Thuny F, Gilstrap L, Arangalage D, Ewer S, Huang S, Deswal A, Palaskas NL, Finke D, Lehman L, Ederhy S, Moslehi J, Salem JE - Electrocardiographic Manifestations of Immune Checkpoint Inhibitor Myocarditis. – **Circulation** - 2021 Nov 2

64. Emile JF, Vaglio A, Cohen-Aubart F, Haroche J - IgG4-related disease and Rosai-Dorfman-Destombes disease - Authors' reply. – **Lancet** - 2021 Oct 2

65. Allaire M, Garcia-Pagán JC, Walter A, Bureau C, Thabut D - Salvage TIPS in cirrhotic patients with variceal bleeding: MELD, lactates and « à la carte » decision. – **Hepatology** - 2021 Dec

66. Gaudric J, Couture T, Arzoine J, Chiche L - Response to \»Comment on 'Short- and Mid-term Outcomes of Cryopreserved Abdominal Aortic Allografts Used as a Substitute for Infected Prosthetic Grafts in 200 Patients'\». - **Eur J Vasc Endovasc Surg** - 2021 Sep

67. Corpechot C - Response to E. Shahini and F. Ahmed Letter JHEPAT-D-21-00372. - **J Hepatol** – 2021 Feb

68. Rudler M, Savier E, Alioua I, Sultanik P, Thabut D - TIPS and liver transplantation should always be discussed together. - **J Hepatol** - 2021 Oct

69. Lemoinne S, Cazzagon N, Chazouillères O, Corpechot C, Arrivé L - Letter: the use of magnetic resonance scores (Anali) for risk stratification in PSC. - **Aliment Pharmacol Ther** - 2021 Jun

70. Guedeney P, Sorrentino S, Mesnier J, De Rosa S, Indolfi C, Zeitouni M, Kerneis M, Silvain J, Montalescot G, Collet JP - Single Versus Dual Antiplatelet Therapy Following TAVR: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. - **JACC Cardiovasc Interv** - 2021 Jan 25

71. Pineton de Chambrun M, Constantin JM, Mathian A, Quemeneur C, Lepere V, Combes A, Luyt CE, Amoura Z - Clarkson's Disease Episode or Secondary Systemic Capillary Leak-Syndrome: That Is the Question! – **Chest** - 2021 Jan;

72. Mathian A, Amoura Z - Response to: 'Patients with lupus with COVID-19: University of Michigan experience' by Wallace et al - **Ann. Rheum. Dis.** - 2021 Mar

73. Voland L, Le Roy T, Debédat J, Clément K - Gut microbiota and vitamin status in persons with obesity: A key interplay. - **Obes Rev** - 2022 Feb

74. Huby T, Gautier EL - Immune cell-mediated features of non-alcoholic steatohepatitis - **Nat. Rev. Immunol.**- 2021 Nov 5

75. Gautier EL, Askia H, Murcy F, Yvan-Charvet L - Macrophage ontogeny and functional diversity in cardiometabolic diseases. - **Semin Cell Dev Biol** - 2021 Nov

76. Oppert JM - Introduction.- **Obes Rev** - 2021 Jul

77. Emile JF, Cohen-Aubart F, Collin M, Fraitag S, Idbaih A, Abdel-Wahab O, Rollins BJ, Donadieu J, Haroche J - **Histiocytosis**. - 2021 Jul

Our founders

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Inserm

SORBONNE UNIVERSITÉ

Our institutional supporters

INVESTIR L'AVENIR

anr agence nationale de la recherche

Our network

iHU FRANCE
Instituts Hospitalo-Universitaires

@IHUICAN

@ICAN_Institute

IHU ICAN

Publication manager: Prof. Stéphane Hatem
Written by: IHU ICAN
Graphic design and production:
Photo credits: IHU-ICAN, RIVA Illustrations CorWave SA, CMDO, Dybopixel, FMSSUS, kasto/Fotolia, endostock, Win Nondakowit, MétaGénoPolis, SCAI, Nadine Suffee, Gorodenkoff Productions OU, Ulf, Martine A Eisenlohr/stock.adobe.com

At the core of health

Pitié Salpêtrière Hospital
Claude Bernard Pavilion
47-83 boulevard de l'Hopital
75013 Paris

IHU ican
Foundation for Innovation
in Cardiometabolism
and Nutrition