2022

Annual Report

At the heart of health

IHU ican

Foundation for Innovation in Cardiometabolism and Nutrition

At the heart of health

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OVERVIEW OF IHU ICAN

JOINT EDITORIAL

Prof. Stéphane Hatem
Chief Executive

Stéphane Barritault
General Secretary

What kind of year was 2022 for IHU ICAN?

Prof. Stéphane Hatem: 2022 saw the preparation, launch and development of key projects for the IHU, thanks to all the hard work carried out by ICAN teams on behalf of our community of clinicians and researchers. Firstly, the IHU confirmed its health data expertise by structuring the entire research data sharing and exchange component of the H2020 Maestria project (Machine Learning and Artificial Intelligence for Early detection of Stroke and Atrial Fibrillation). This major European project involving 18 academic and industry partners seeks to develop new approaches enabling the early detection of atrial cardiomyopathy in order to improve care management and identify novel therapeutic targets to develop personalised medicine for atrial fibrillation and strokes. Maestria aims to create the first integrative digital platform for diagnosing atrial cardiomyopathy. This platform will be designed to improve diagnostic accuracy in order to increase treatment efficacy and efficiency, while also preventing atrial cardiomyopathy complications such as atrial fibrillation and strokes. The project involves circulating research data among teams based in countries that do not all share the same regulations and teams that work with different digital systems. Regulatory and interoperability issues are therefore a key concern for the whole consortium. ICAN is addressing this situation and coordinating the process to remove barriers hampering the exchange of research data within the project. A workshop in June 2022 formed a key part of these coordination efforts.

> **“REGULATORY AND INTEROPERABILITY ISSUES ARE THEREFORE A KEY CONCERN FOR THE WHOLE CONSORTIUM”**

IHU ICAN research laboratory

Through an intensive two days' work on the interoperability of collected data, it was possible to identify the main challenges for each data type (imaging, ECG, omics and clinical data) and devise practical strategies to address each identified difficulty. This work for MAESTRIA showcased the full extent of ICAN's efficiency and consolidated its teams' expertise in the use of big data in research.

MAESTRIA SHOWCASED THE FULL EXTENT OF ICAN'S EFFICIENCY

This expertise was pivotal to setting up the ICAN I/O data platform, which marks a new addition to the services offered by the IHU. The new platform further enhances ICAN's ability to use health data in research, allowing an even more finely honed response to medical and research teams' requirements. ICAN I/O offers expertise focused on multi-omics and clinical data analysis and integration, incorporating aspects of data governance and management. The platform embodies the latest technologies and the use of robust algorithms to achieve research objectives through a collaborative and holistic approach incorporating multi-omics and statistical analysis technologies. Also on the subject of major research projects that generate big imaging and omics data, the IHU has acquired servers able to fully and securely meet storage requirements for generated data. These servers, hosted by Sorbonne University's SACADO Joint Service Unit (UMS), were acquired and installed with support from our founder, Sorbonne University.

This new equipment gives IHU ICAN significant autonomy over health data and allows it to conduct its community's ambitious projects.

In 2022, substantial funding of €1,500,000 was secured through the Sésame Filières call for proposals issued by the Ile-de-France (Greater Paris) Region and Bpifrance to create an interoperable and multidisciplinary haemodynamic cardiovascular imaging infrastructure with major appeal to industry: the Heart-Aorta Atlas for the general population. The successful outcome of this competitive call for proposals is further proof of the IHU's expertise in developing large-scale projects, particularly those relating to imaging and big data in research. To provide a full assessment of 2022, I would also like to highlight the contribution made by the IHU's medical and scientific community to ensuring the institute's operational success. The IHU fully met its remit of incubating projects and played a key role in maturing them. To provide just a few specific examples, IHU ICAN developed successful collaborations with Prof. Pascal Leprince's heart surgery department, Prof. Estelle Gandjbakhch's rhythmology unit and Prof. Philippe Charron, coordinator of the reference centre for hereditary heart disease.

Congratulations also go to ICAN executive committee member, Dr Antonio Gallo, who has been appointed to replace Prof. Eric Bruckert as Head of the Endocrinology, Metabolism and Cardiovascular Risk Prevention Department.

We must furthermore congratulate IHU executive committee member, Prof. Irène Netchine, for her remarkable work on parental imprinting and commitment to young patients and their families. Her efforts have been rewarded with a prestigious publication in the journal Clinical Epigenetics and a patent filed on a new cellular approach. Parental imprinting is an epigenetic mechanism leading to the monoallelic expression of a subset of genes according to their parental origin. In collaboration with the ICAN BioCell-iPS platform, Prof. Irène Netchine's team developed a new cellular approach using pluripotent stem cells to model the pathophysiology of parental imprinting diseases.

2022 was also a highly productive year for publications, with 520 publications in total. Of particular note are the numerous prestigious publications pertaining to the MetaCardis patient cohort. This success is a fitting reward, marking the culmination of a decade's hard work by IHU ICAN teams. MetaCardis is a major European project investigating the role of gut microbiota in cardiometabolic disease development, to which the IHU ICAN has allocated significant funding and resources through the Investment for the Future Programme (PIA) grant.

2022 WAS ALSO A HIGHLY PRODUCTIVE YEAR FOR PUBLICATIONS, WITH OVER 520 PUBLICATIONS IN TOTAL

The final point to raise in this review of the year is that two IHU ICAN researchers appear in the Clarivate ranking of the world's top 100 most cited researchers.

ICAN BioCollection

Stéphane Barritault: It should also be noted that collaboration between the general secretaries of the IHU France alliance comprising 6 IHUs (Foresight, IHU Strasbourg, Imagine, Paris Brain Institute, IHU Liryc and ICAN) was stepped up in 2022. Through this cooperation, it has been possible to share experience of clinical research, particularly with regard to applying personal data regulations.

PERMANENT STAFF ARE ESSENTIAL FOR CONDUCTING LONG-TERM RESEARCH PROGRAMMES

IHU ICAN has instigated a discussion with the French data protection authority (CNIL) on this topic, so that work can be carried out jointly on arrangements for using health data in research through domestic or international projects.
Cooperation between IHUs in the IHU France alliance will undoubtedly lead to ambitious cross-disciplinary research projects, the first of which on digital twins is currently being set up with a leading industrial partner in the field.
As regards the life of the IHU, the Foundation's new articles of association have been approved by the Minister for Higher Education and Research and the rules of procedure have also been reviewed to optimise the way the IHU is run.
In terms of HR matters, we have implemented a job security policy encouraging the use of open-ended employment contracts wherever justifiable. Permanent staff are essential for conducting long-term research programmes and ensuring that employees are involved in IHU projects over long periods.
From a financial perspective, we continued to structure the IHU's accounting and purchasing processes to support the scientific timetable (2019-2023). It should also be noted that 2022 was an exceptional year in terms of developing sponsorship activity, with over €2 million pledged in donations, which will contribute to key projects in the coming years.

As part of the review of 2022, we should also mention the government's announcement of a new round of assessments for first-wave IHUs. These assessments are of critical importance to all IHUs, as they are crucial for securing additional funding to cover overheads and continue projects led by the IHUs. While continuing to set up and develop scheduled projects, IHU ICAN has made changes to its structure with the introduction of a steering committee tasked with reviewing the first decade and showcasing its results in the renewal application. Preliminary work has been very encouraging, particularly since IHU ICAN's key scientific areas and the focus of measures taken in recent years are consistent with the France 2030 investment plan aimed at developing innovation in the health sector based on AI and big data.

What do you consider to be the opportunities and key challenges facing IHU ICAN in 2023?

Prof. Stéphane Hatem
IHU ICAN has assumed a leading role in the use of health data in research due to the expertise its teams have developed through setting up and implementing major domestic and European projects. It is therefore essential for the IHU to take part in further national consortia, particularly those relating to health data and AI.
ICAN must fulfil its role as a partner and facilitator for an extended scientific and medical community in the field of cardiometabolism. Its ability to structure cohorts is a further indisputable strength, paving the way for participation in patient population phenotyping projects.
IHU ICAN provides a full range of cutting-edge services and expertise, putting members of its community in a leading position to take part in major academic and industry projects.
One of the key challenges facing the IHU will be to create a unique cardiovascular and liver imaging atlas for France. The aim of this “ICONIC” project is to investigate the causes of cardiovascular and metabolic diseases, including among French people aged under 40. A substantial body of convergent data currently suggest that ageing mechanisms and cardiovascular and metabolic pathophysiological mechanisms start earlier in life than previously foreseen.
The first half of life, focused on learning basic skills and reproduction, is a key period and 40 is a pivotal age from which certain degenerative, oncogenic and inflammatory processes present.

Medical imaging now plays a key role in understanding, early detection, prognostic assessment and personalised patient care. However, very little research has been conducted on subclinical multi-organ impairments in young patients, since most large international cohorts have recruited subjects aged over 40.

THE ABILITY TO STRUCTURE COHORTS IS AN INDISPUTABLE STRENGTH

This new knowledge on pathophysiological processes that are now measurable *in vivo* due to non-invasive imaging paves the way for a new research paradigm whose basis no longer lies in the traditional deterministic relationship between clinical data and an event, but includes an analysis of mechanistic parameters involved from the early stages, potentially providing new diagnostic, prognostic and therapeutic targets and a missing link with medical breakthroughs. However, the anticipated improvements offered by an advanced phenotypic study are only meaningful if it is performed with the relevant population and new imaging and data processing technologies are used.
The ICONIC project presents an organisational and financial challenge, with further funding required in addition to the funds already raised and a significant workload for ICAN Imaging platform teams (research MRI and Core Lab) spanning several years. 2023 is a key year in preparing for this ambitious project.
These major challenges reflect the IHU's priorities and ambitions for 2025/2030, which will be presented in the IHU's assessment and renewal application.

Stéphane Barritault

In 2023, the IHU must make every effort to achieve the goals of its financial trajectory with support from its founders.

> **THE IHU IS IN THE PROCESS OF FORGING PROMISING COLLABORATIONS WITH PUBLIC AND PRIVATE ENTITIES IN THE UNITED ARAB EMIRATES**

To establish its status as a centre of excellence for research, care, training and research valorisation in the field of cardiometabolic diseases and nutrition, IHU ICAN has embarked on a quality programme aimed at securing ISO 9001 international certification of the fitness of its management system to provide services meeting its partners' requirements. This process will also help strengthen partnerships between the private and public sectors, thus speeding up the transfer of innovations for the benefit of patients. All teams are heavily involved in this certification project.

A further key challenge for 2023 prioritised by the IHU is to strengthen partnerships with pharmaceutical players, whether large groups, intermediate-sized enterprises or medical device specialists, as well as with biotech or medtech SMEs, particularly those involved in eHealth, and also with other research centres around the world. The partnership in place with the cardiometabolic health, diabetes and obesity network (CMDO) in Quebec since 2014 is a model we would like to replicate in other countries. Moreover, the IHU is currently in the process of forging promising collaborations with public and private entities in the United Arab Emirates in the fields of NASH and atrial fibrillation.
Projects have gained considerable momentum in the past two years and IHU teams are working with great agility to support investigators with incubating, structuring, conducting and valorising their research projects.

Research laboratory - IHU ICAN

2022 KEY FIGURES

€6.1 million
budget

56 employees

BASIC AND APPLIED RESEARCH

221 researchers

11 research teams

7 cutting-edge scientific research platforms

520 scientific publications
including 169 with an impact factor >10

30 patents
in the portfolio

CLINICAL CARE AND RESEARCH

168 doctors

15 clinical teams

1 Clinical Research Division comprising
- 1 clinical investigation platform specialising in cardiometabolism and nutrition
- 1 cardiometabolic imaging platform (MRI and Core Lab)

54 clinical studies in progress
of which 28 are commercial and 26 are academic, including:
- 19 hepatology studies
- 14 rhythmology studies
- 9 endocrinology/diabetes studies
- 6 cardiology studies
- 4 nutrition studies

6 reference centres for rare diseases

LDL-apheresis treatment

METABOLIC DISEASES

Metabolic diseases present a major public health challenge and are the leading cause of mortality and morbidity in France. Case numbers are continually rising due to an ageing population and changing lifestyles, resulting in a genuine epidemic of these chronic diseases.

IHU ICAN HAS ESTABLISHED AN INTEGRATED MODEL, FROM RESEARCH TO CARE

A concerning rise in metabolic diseases

The distinguishing feature of these diseases is that they progress silently throughout the course of a lifetime and generally present in their late stages as acute episodes potentially threatening the lives of patients or leading to a sudden decline in quality of life. Although significant progress has been made on treating cardiovascular and metabolic diseases in recent decades, this by no means diminishes the huge challenge faced, and there is considerable room for improvement.

IHU ICAN was founded to meet this challenge and has established an integrated model, from research to care, to speed up scientific and medical progress.

IHU ICAN teams have based their approach on the principle that metabolic, nutritional and heart diseases are connected, and therefore a rethink of care and research is required to incorporate a multidisciplinary and multi-organ dimension.

Cardiovascular diseases

These diseases are the world's top cause of death for people aged under 65, claiming the lives of 17.7 million people per year and representing 31% of all-cause mortality. 54% of deaths are among women. Cardiometabolic diseases are risk factors for developing severe forms of many other diseases, as observed with COVID-19.

To meet these public health challenges, IHU ICAN is developing an innovative translational research model focused on new interfaces between organs: the heart, microbiota, adipose tissue, liver and immune system are very promising avenues for improving understanding of the pathophysiological mechanisms of cardiometabolic disease development.

Diabetes

Global prevalence of diabetes has quadrupled since 1980, affecting 1 in 20 individuals worldwide. It is the ninth leading cause of death globally (1.5 million deaths a year) and the number of deaths due to diabetes has risen 70% since 2000. In France, over 3.7 million people take diabetes medication. This disease leads to several complications: blindness, kidney failure, lower limb amputation, heart failure, etc.

Obesity

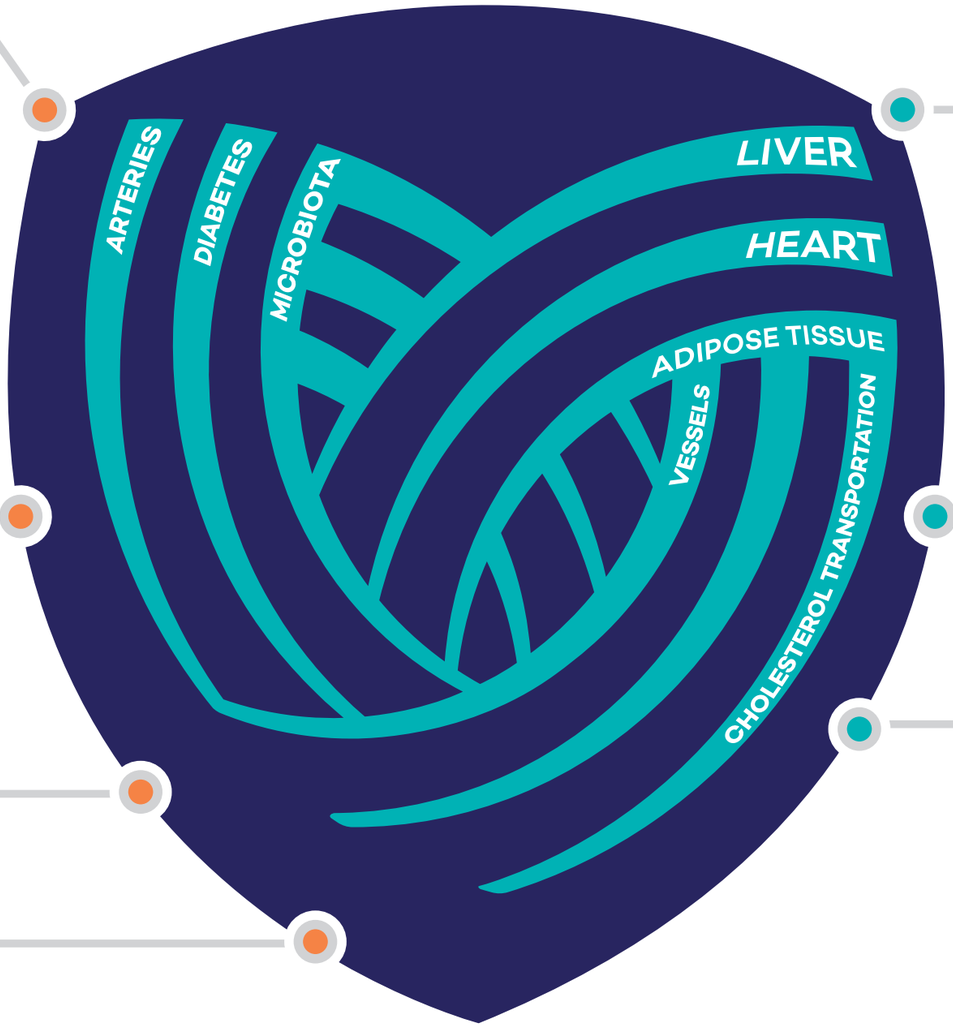
Global obesity rates have tripled since 1975, with 13% of adults suffering from obesity worldwide and 39% are overweight. In France, obesity affects 17% of adults. Increasing numbers of children and adolescents also suffer from this condition. In the under-18 age bracket, it affects 16% of boys and 18% of girls.

Liver diseases (non-alcoholic steatohepatitis)

Also known as “fatty liver disease” or “soda disease”, non-alcoholic steatohepatitis or “NASH”, is a chronic disease caused by the accumulation of fat in the liver (steatosis) combined with metabolic risk factors (obesity, type 2 diabetes, etc.) but not linked to excessive alcohol consumption. Rates of NASH are continually rising globally. The number of people suffering from metabolic steatosis is growing sharply, and will continue to rise in the years to come, due in particular to the upsurge in cases of type 2 diabetes and obesity worldwide. It affects 18% of the adult population in France (25% globally, 32% in the United States).

THE IHU'S ECOSYSTEM

IHU ICAN brings together a multidisciplinary community of basic and clinical research experts united in pursuit of a common goal: tackling metabolic diseases.



RESEARCH UNITS

UMR 938: Adipocyte, Lipodystrophy, Diabetes and Glucocorticoid

UMR 1138: Metabolic Diseases, Diabetes and co-morbidities

UMR 1146: Cardiovascular imaging and Artificial intelligence

UMR 1166: Cardiomyopathy, Atherothrombosis, Cardiac arrhythmias and Lipid transportation Microbiota

UMR 1269: Nutrition, Microbiota, Adipose tissue and Data Integration

CLINICAL TEAMS

ARCHIMEDE DMU (Medical-University Department)
Pitié Salpêtrière Hospital Group
- Cardiology Department
- Cardiovascular and thoracic surgery department
- Department of intensive care medicine
- Endocrinology department
- Diabetes department
- Endocrinology and reproductive medicine department
- Endocrinology, metabolism and cardiovascular disease prevention department
- Unit for thyroid disorders and endocrine tumours
- Internal medicine department
- Nutrition department

Saint-Antoine Hospital Group
- Cardiology department
- Endocrinology, diabetes and reproductive medicine department

CARDIOVASCULAR AND THORACIC IMAGING UNIT (DIAMENT DMU)

REFERENCE CENTRES FOR RARE DISEASES
- Prader-Willi syndrome and other rare obesities - PRADORT
- Hereditary or rare cardiac diseases
- Rare insulin-secretion and insulin-sensitivity diseases
- Inflammatory diseases of the biliary tract and autoimmune hepatitis
- Rare endocrine diseases of growth and development
- Rare gynaecological diseases

CARDIOMETABOLISM AND NUTRITION FOUNDATION

7 CUTTING-EDGE SCIENTIFIC PLATFORMS

ICAN Omics
Lipidomics

ICAN Omics
Metabolomics

ICAN BioCollection
Biobanking

ICAN BioCell
iPS

ICAN BioCell
Human Liver Biology

ICAN I/O
Data Sciences

ICAN BioCell
Flow Cytometry

1 CLINICAL RESEARCH DIVISION

ICAN Clinical Investigation
Cardiometabolic Diseases

ICAN Imaging
MRI - Core Lab

- Innovation and Research Valorisation Division
- Legal, Compliance and Data Policy Division
- Administration, HR and Finance Division
- Communication and Sponsorship Division

IHU ICAN teams

Research and clinical teams

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS · Inserm · SORBONNE UNIVERSITÉ

RESEARCH TEAMS

11 expert cardiometabolic research teams

Research Unit 1166 for Cardiovascular and Metabolic Diseases
Prof. Stéphane Hatem
This joint research unit set up in 2014 is wholly devoted to research into cardiovascular and metabolic diseases focused on four key areas: atherothrombosis and coronary heart diseases, the genomics of cardiomyopathies and heart failure, atrial fibrillation and cardiac arrhythmias, lipids and atherosclerotic vascular diseases.

- **Team 1** - Genomics and Pathophysiology of Myocardial Disease
  Prof. Philippe Charron

- **Team 2** - Atherothrombosis and Applied Pharmacology
  Michel Zeitouni

- **Team 3** - Molecular and Cell Plasticity in Cardiovascular Diseases
  Sophie Nadaud and **Elise Balse**

- **Team 4** - Cellular and Systemic Lipid Metabolism in Cardiometabolic Diseases
  Wilfried Le Goff

- **Team 5** - Mononuclear Phagocytes in Cardiometabolic Diseases
  Philippe Lesnik

UMR 1166 research laboratory

UMR 1146 - Biomedical Imaging Laboratory (LIB)
CNRS - INSERM
Team - Cardiovascular Imaging
Nadjia Kachenoura (INSERM Research Director)
Development of new cardiac and vascular imaging biomarkers combining cardiovascular phenotypes, development and validation of cardiac and vascular image processing software.

Research Unit 938 - Saint-Antoine Research Centre
3 of the 13 teams from this unit are part of IHU-ICAN

- **Team 9** - Lipodystrophies, Metabolic and Hormonal Adaptations, and Ageing
  Prof. Bruno Fève

- **Team 11** - Metabolic Fibro-inflammatory and Liver Bile Diseases
  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

CLINICAL TEAMS

IHU ICAN brings together internationally renowned clinical experts.

ARCHIMEDE MEDICAL-UNIVERSITY DEPARTMENT (DMU)
Prof. Richard Isnard
The ARCHIMEDE DMU combines clinical departments and units involved in the treatment and care of acute and chronic cardiovascular and metabolic diseases, as well as certain rare conditions.

Pitié-Salpêtrière Hospital Group
Institute of Cardiology
- Cardiology Department
  Prof. Jean-Philippe Collet
- 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 Hartemann
- Endocrinology and Reproductive Medicine Department
  Prof. Philippe Touraine
- Endocrinology, Metabolism and Cardiovascular Disease Prevention Department
  Dr Antonio Gallo
- Functional Unit for Thyroid Disorders 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

Clinical Investigation Centre (CIC) Paris-East
Prof. Christian Funck Brentano

Human Nutrition Research Centre (CRNH)
Prof. Jean-Michel Oppert

CARDIOVASCULAR AND THORACIC IMAGING UNIT ICT (DIAMENT DMU)
Prof. Alban Redheuil
The ICT is the cardio-radiology unit at Pitié Salpêtrière, specialising in cardiac, vascular and thoracic imaging. The team is involved in research through IHU ICAN's ICAN IMAGING platform.

IHU ICAN MRI platform

GOVERNANCE

Board of Trustees

The board of trustees, consisting of 13 members, 3 founding members, 5 qualified persons, 3 private-sector representatives and 2 representatives elected by associate professors, sets the IHU's overall policy.

President of the Board of Trustees
Thierry Tuot, Councillor of State (replaced by Prof. Catherine Boileau on 29 March 2023)

Founders' Representatives
Nathalie Drach-Temam, President of Sorbonne University
Nicolas Revel, Chief Executive of the Paris Public Hospital Network (AP-HP)
Didier Samuel, President and Chief Executive of INSERM

Permanent Invitees
Elli Chatzopoulou, Director of Partnerships and External Relations, INSERM
Milan Lazarevic, Clinical Research and Innovation Director, AP-HP
Bruno Riou, Dean of the Faculty of Medicine, Sorbonne University

Qualified Persons
Catherine Boileau, University Professor/Hospital Practitioner, AP-HP
Claudine Canale, President of the Poids Plumes Association
Ehrlich Dusko Stanislav, Director of Research, INRA
Jessica Leygues, CEO MEDICEN, Paris Region

Private Sector Representatives
Laurence Comte-Arassus, GE Healthcare, Chief Executive, FBFA zone, Representative for SNITEM
Pierre Sonigo, SEBIA, Director, R&D and Medical Affairs
Philip Janiak, Chief Executive of Corteria Pharmaceuticals

Representatives of Researchers and Associate Professors
Bruno Fève, Head of Research Unit 938
Corinne Frère, Lecturer/Hospital Practitioner, Biological Haematology, AP-HP

Jessica Leygues
CEO of the Paris Region Medicen cluster and member of the IHU ICAN Board of Trustees

"Medicen is the health competitiveness cluster for the Ile-de-France Region. Through its network of health innovation stakeholders, it identifies clinical and academic needs with a view to proposing future solutions and supporting the development of innovative diagnostic and therapeutic solutions.
Thanks to Medicen's involvement in the ICAN Board of Trustees, the IHU has access to the cluster's network in the 3 healthtech sectors of medtech, biotech and eHealth, and its capacity to coordinate and support ecosystems. Health data provided the focus of a recent collaboration between Medicen and the IHU at a conference on big data and AI organised by IHU ICAN. Medicen's president, Christian Deleuze, took this opportunity to present the cluster's recommendations on financial aspects of health data use. Health data are a key tool in transforming health systems, enabling precision, preventive and personalised medicine. However, certain barriers prevent the innovation potential of these data from being fully tapped and slow the development of digital solutions. Measures are urgently needed to enable France to use the health data at its disposal for the benefit of patients.
To that end, the conference sought to bring together all partners involved in regulatory, ethical, financial and technical aspects of health data use, and provided an opportunity to consider effective solutions for revealing France's potential in relation to health data."

Executive Committee (COMEX)

The COMEX consists of the chief executive, the general secretary, the heads of the IHU's internal divisions and one community representative per key strategic area. The Director of the Pitié-Salpêtrière Hospital Group and the Medical Director of the ARCHIMEDE DMU are permanent invitees. The COMEX is tasked with helping the chief executive, in particular, to define the IHU's strategy and scientific priorities, and also with all other aspects of management.

Prof. Judith Aron-Wisnewsky, Endocrinology and Metabolism
Dr Olivier Bourron, Diabetes
Loïc Carbadillo, Director of Research AP-HP Sorbonne University
Prof. Philippe Charron, Head of the Genomics and Pathophysiology of Myocardial Diseases research team, UMR 1166, and Director of the Reference Centre for Cardiomyopathies and Hereditary Cardiac Rhythm Disorders
Prof. Alain Combes, Intensive Care Medicine
Dr Laurie Dufour, Cardiology and Vascular Diseases
Prof. Bruno Fève, Director of Research Unit 938 – Saint-Antoine Research Centre
Dr Antonio Gallo, Cardiovascular Disease Prevention
Prof. Estelle Gandjbakhch, Cardiology and Vascular Diseases
Prof. Richard Isnard, Cardiology and Vascular Diseases
Wilfried Le Goff, Head of the Cellular and Systemic Lipid Metabolism in Cardiometabolic Diseases team - UMR 1166
Prof. Irène Netchine, Physiology - Paediatric Functional Investigation
Prof. Vlad Ratziu, Gastroenterology and Hepatology
Prof. Alban Redheuil, Cardiovascular Imaging

Prof. Estelle Gandjbakhch
Cardiology and Vascular Diseases; Head of the Rhythmology Unit (Pitié Salpêtrière Hospital Group)

"IHU ICAN helps project leaders, who may be doctors, researchers or nurses, to set up their projects. In addition to its expertise in developing projects and seeking funding, ICAN offers access to opportunities for academic and industry collaborations, which are key drivers of innovation in research projects."

Dr Antonio Gallo
Lecturer - Lipidology and Cardiovascular Prevention Unit - Department of Nutrition - Pitié-Salpétrière Hospital Group

"IHU ICAN brings together a large community of experts, researchers and clinicians focused on metabolic diseases. This encourages interdisciplinary collaborations by breaking down silos in research. It also enables links to be promoted with business for the purposes of translational research."

IHU Board

The IHU Board consists of the IHU Chief Executive as chair; the General Secretary; the Dean of Sorbonne University Faculty of Medicine; the directors and team leaders of the UMRs involved in ICAN; the Medical Director of the ARCHIMEDE DMU; and the department heads of this DMU involved in ICAN's clinical activities.
Its objective is to strengthen cohesion within the IHU's medical and scientific community and to allow a flow of information between the teams to ensure overall consistency. The IHU Board provides a forum for discussing and sharing strategic priorities and the IHU's scientific policy.

Prof. Zahir Amoura, Head of the Internal Medicine Department at Pitié-Salpêtrière Hospital Group
Elise Balse, Head of the Molecular and Cellular Plasticity in Cardiovascular Diseases team – UMR 1166
Prof. Philippe Charron, Head of the Genomics and Pathophysiology of Myocardial Diseases research team, UMR 1166, and Director of the Reference Centre for Cardiomyopathies and Hereditary Cardiac Rhythm Disorders
Prof. Laurent Chiche, Head of the Cardiovascular Surgery Department at Saint-Antoine Hospital

Prof. Sophie Christen-Maitre, Head of the Endocrinology, Diabetes and Reproductive Medicine Department at Saint-Antoine Hospital
Prof. Karine Clément, Head of UMR 1269, Nutriomics - Nutrition and Obesities
Prof. Ariel Cohen, Head of the Cardiology Department at Saint-Antoine Hospital
Prof. Jean-Philippe Collet, Head of the Cardiology Department at Pitié-Salpêtrière Hospital Group
Prof. Alain Combes, Head of the Intensive Care Department at Pitié-Salpêtrière Hospital Group
Prof. Bruno Fève, Director of Research Unit 938 – Saint-Antoine Research Centre
Fabienne Foufelle, Head of the Metabolic Diseases, Diabetes and Comorbidities team - UMR 1138, Cordeliers Research Centre
Prof. Christian Funck-Brentano, Manager of the Clinical Investigation Centre (CIC) Paris-East
Dr Antonio Gallo, Head of the Endocrinology, Metabolism and Cardiovascular Disease Prevention Department at Pitié-Salpêtrière Hospital Group
Prof. Agnès Hartemann, Head of the 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 ARCHIMEDE DMU
Nadjia Kachenoura, Head of the Cardiovascular Imaging Team, UMR 1146
Wilfried Le Goff, Head of the Cellular and Systemic Lipid Metabolism in Cardiometabolic Diseases team - UMR 1166
Prof. Laurence Leenhardt, Head of the Functional Unit for Thyroid Disorders and Endocrine Tumours
Prof. Pascal Leprince, Head of the Cardiac Surgery Department at Pitié-Salpêtrière Hospital Group
Elise Lesnik, Head of the Mononuclear Phagocytes in Cardiometabolic Diseases team – UMR 1166
Sophie Nadaud, Head of the Molecular and Cellular Plasticity in Cardiovascular Diseases team – UMR 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 and the Human Nutrition Research Centre (CRNH)
Prof. Christine Poitou Bernert, Nutrition - Reference Centre for Rare Genetic Obesities
Prof. Alban Redheuil, Head of the Cardiovascular Imaging Unit at Pitié-Salpêtrière Hospital Group
Prof. Bruno Riou, Dean of the Faculty of Medicine
Prof. Philippe Touraine, Head of the Endocrinology and Reproductive Medicine Department
Prof. Corinne Vigouroux, Reference Centre for Rare Insulin-Secretion and Insulin-Sensitivity Diseases (PRISIS)
Dr Michel Zeitouni, Head of the Systemic and Cellular Lipid Metabolism in Cardiometabolic Diseases team UMR 1166

Scientific Advisory Board

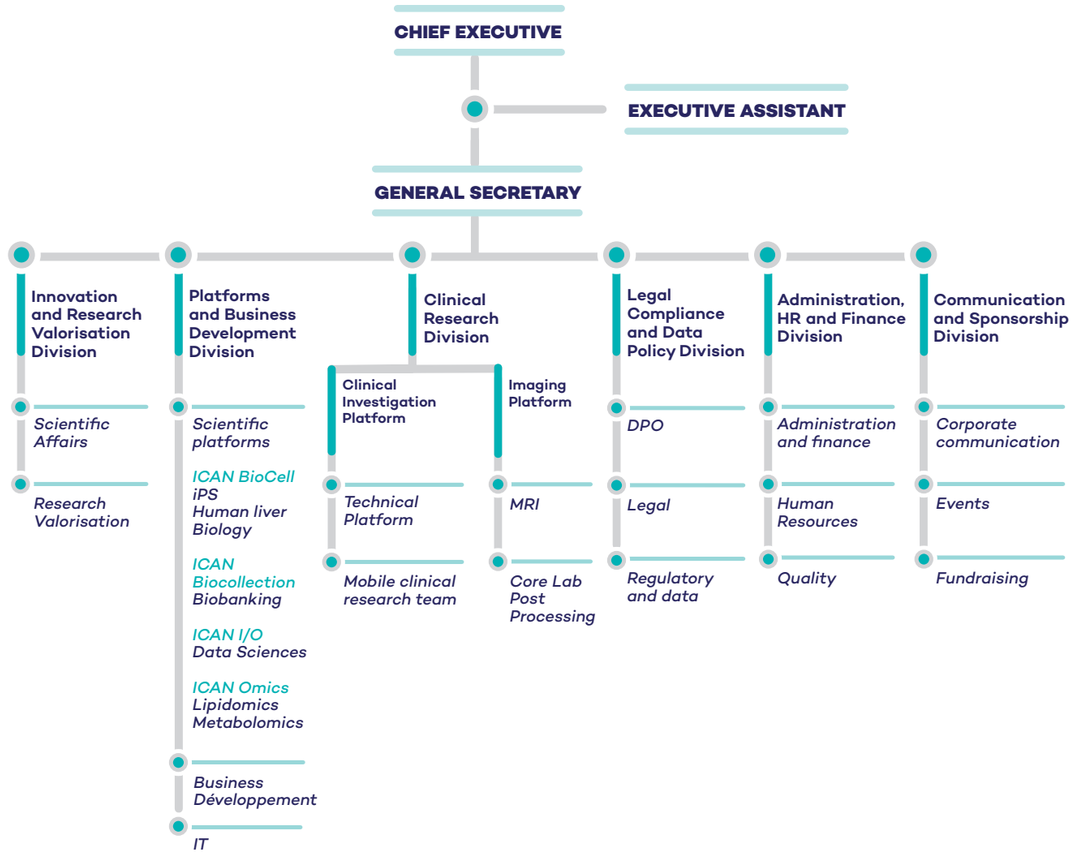
The scientific advisory board offers expert, critical and constructive oversight of ICAN's scientific strategy. It consists of 6 external members who are highly recognised within the international scientific community in the fields of cardiometabolism and nutrition. This scientific governance body, appointed by the Board of Trustees, is consulted on the IHU's key scientific priorities and annual action programme.

Prof. André Carpentier, Director of the "Diabetes, obesity and cardiovascular complications" key research area, Faculty of Medicine and Health Sciences at the Université de Sherbrooke, Canada
Prof. Arnold Von Eckardstein, Professor of Clinical Biochemistry, Laboratory Medicine and Pathology, University Centre for Laboratory Medicine and Pathology (UZL), Switzerland
Prof. 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, Chair of the SAB, Professor of Medicine and Head of Experimental Cardiology, University of Louvain, Belgium
Prof. Rozemarijn Vliegenthart, Radiologist and Professor of Cardiothoracic Imaging, University Medical Center Groningen, Netherlands.

GOVERNANCE

Senior Management and Executive Committee
Prof. Stéphane Hatem has been IHU ICAN's chief executive since 2018. The chief executive oversees the general management of the IHU and is assisted by a general secretary, Stéphane Barritault, who is responsible for the operational management of the institute. These two men at the helm of the IHU are supported by an executive committee with 6 members:

Stéphane Commans, Innovation and Research Valorisation Division
Maud Decraene, Legal, Compliance and Data Policy Division
Jeanne Haidar, Clinical Research Division
Ludovic Le Chat, Platforms and Business Development Division
Stéphanie Lapous, Administration, HR and Finance Division
Francine Trocmé, Communication and Sponsorship Division



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LIGHTS

IHU ICAN CONTRIBUTES TO THE IHU FRANCE ALLIANCE WHITE PAPER

The alliance's first white paper, produced jointly by the 6 IHUs (FORESIGHT, IHU ICAN, Paris Brain Institute, IMAGINE, LIRYC and IHU Strasbourg) forming the IHU France alliance, was published in February 2022, presenting ideas and key areas for development aimed at perpetuating the IHU model and enhancing the IHUs' performance.

Ten years after they were set up by the French government, the IHUs (Hospital-University Institutes) have proven their agility, responsiveness and innovation capacity when faced with major public health challenges.
An "IHU model" has since developed and demonstrated its effectiveness by enabling the emergence of major new discoveries benefiting patients. In the health sector, France now has all the necessary tools to put it at the forefront of innovation.

Coordinating this expertise, the 6 IHUs in the IHU France alliance pool their efforts to consolidate this model and constantly increase its impact on public health, while also placing France at the cutting edge of tomorrow's medicine. Drawing on the combined experience and lessons learned by each IHU in its scientific field, the IHU France alliance has outlined a set of proposals aimed at enhancing the performance of the IHU model in its white paper:

1- **FASTER and LOWER-RISK** transfer of innovations to patients through the IHUs
- **Proposal no. 1:** help start-ups get off the ground by facilitating equity investment by IHUs
- **Proposal no. 2:** speed up negotiations with private partners using the full potential of the single mandate

2- **ENHANCING the role of IHUs** as third places for experimentation and international appeal
- **Proposal no. 3:** share IHUs' successes and lessons learned to promote innovation in France
- **Proposal no. 4:** position IHUs as recognised centres for trialling digital health solutions with a crossover between care and research
- **Proposal no. 5:** encourage sponsorship of clinical trials by all IHUs in coordination with university hospitals and research bodies

3- **ROOTING** the IHUs permanently in the French research and innovation landscape
- **Proposal no. 7:** secure long-term funding for IHUs through a baseline endowment
- **Proposal no. 8:** allow IHUs to apply for calls for proposals on their own behalf

"In 10 years, the IHUs have demonstrated the full potential of this new French medical research model to speed up innovation by developing interdisciplinary collaborations and forging links between the academic and private sectors. IHU ICAN is proud of its contribution to shaping the IHUs' first white paper that celebrates achievements while also engaging with the public authorities on barriers hampering the IHUs' operations, thus enabling future successful applicants for the IHU label (announced in May 2023) to benefit from this feedback. The white paper also sets out an ambitious programme of innovative future projects including a collaboration between the IHUs on developing multi-organ digital twins."

Stéphane Barritault
General Secretary

IHU ICAN AT EXPO 2020 IN DUBAI

IHU ICAN took part in a lecture series organised by the French Healthcare Association as part of the Health Research and Innovation fortnight in the French Pavilion at Expo 2020 in Dubai.

Its Chief Executive, Stéphane Hatem, General Secretary, Stéphane Barritault, and Head of the Innovation and Research Valorisation Division, Stéphane Commans, presented the IHU model aimed at improving the management of cardiometabolic disorders (cardiovascular diseases, diabetes, obesity, NASH/soda disease, etc.) through a multidisciplinary and translational approach. ICAN is forging links with public and private entities in the United Arab Emirates so that they can benefit from its expertise on researching metabolic diseases, whose prevalence is rising sharply in the region. To increase its international reach and help secure academic and private sector partnerships abroad, IHU ICAN has also joined French Healthcare, an association promoting French health expertise worldwide.

MAESTRIA WORKSHOP

On 7 and 8 June 2022, international partners in the European H2020 MAESTRIA (Machine Learning and Artificial Intelligence for Early Detection of Stroke and Atrial Fibrillation) project met in Paris to discuss the interoperability of collected data, which is critical to the project's success.

These 2 working days provided project stakeholders with an opportunity to expand on their discussions with a view to identifying key interoperability challenges for each data type (imaging, ECG, omics and clinical data) and agreeing on the next dedicated committees to address each identified issue.
Led by Prof. Stéphane Hatem, MAESTRIA is a major European atrial cardiomyopathy project involving a consortium of 18 academic and industry partners at the cutting edge of research and medical care for these conditions. MAESTRIA seeks to meet the key challenges of data integration and personalised medicine with the focus on atrial cardiomyopathy, atrial fibrillation and strokes.

The project aims to create multi-parametric digital tools using a new generation of biomarkers that integrate artificial intelligence (AI) processing and big data from cutting-edge imaging, electrocardiography and omics technologies. Digital twin technologies and a data integrator combining biophysics and AI will be used to generate virtual models of human atria using specific patient data.

NEW SERVERS TO SUPPORT GLOBAL SCIENTIFIC PROJECTS

With support from its founder, Sorbonne University, two computation servers and two disk arrays dedicated to IHU ICAN projects were installed in the SACADO service unit in October 2022.

This equipment is split across 2 different sites for security reasons, with a second disk array used for backup replication.
These new servers significantly increase the security, efficiency and resilience of IHU ICAN's information system. The chosen configuration also enables structuring in accordance with GDPR requirements, which is an essential requirement for collecting, storing and processing personal health data.
In practice, eight virtual machines have been configured for the two computation servers, enabling the deployment of essential application software for IHU ICAN's technological platforms.
These machines are mainly used by the ICAN Imaging (MRI, Core Lab) and ICAN BioCollection and Omics (lipidomics, metabolomics) platforms to perform their activities.
They also now host backups of raw data from the ICAN Omics platforms' mass spectrometers and from the ICAN CRB business software. These platforms are involved in numerous studies conducted by the IHU and its scientific community. Having previously come close to saturation, storage capacities are now fully in line with current requirements and offer sufficient space for both prospective and scheduled projects.
The new servers have immediately proved vital in the OPTIM-HCM hospital clinical research programme coordinated by Prof. Philippe Charron and sponsored by the Paris Public Hospital Network (AP-HP). IHU ICAN's ICAN Imaging platform has been chosen as the central post-processing Core Lab for this multi-centre project tasked with assessing heart function parameters and performing delayed enhancement on over 2,000 MRIs. In addition to its scientific significance, the ICAN Core Lab's involvement in a study of this scale clearly reflects the status of the ICAN Imaging platform as a leading cardiometabolic imaging research centre in France.
The servers' deployment will, in particular, secure the IHU's capacity to implement future strategic projects.

Ludovic Le Chat
Head of the Platforms and Business Development Division

"Sorbonne University has acquired and supplied ICAN with two servers with sufficient storage capacity to cover the next 5 to 10 years. Their configuration was completed in January 2023 with assistance from teams at SACADO and the Faculty of Medicine IT Department. These new servers increase the security, efficiency and resilience of our IT system and enable structuring in accordance with GDPR requirements. These servers host application software that is essential to the ICAN Imaging platform, the biological resources centre, and the two Omics platforms. They are used for the OPTIM-HCM hospital clinical research programme, a multi-centre study to assess heart function parameters and delayed enhancement on over 2,000 MRIs."

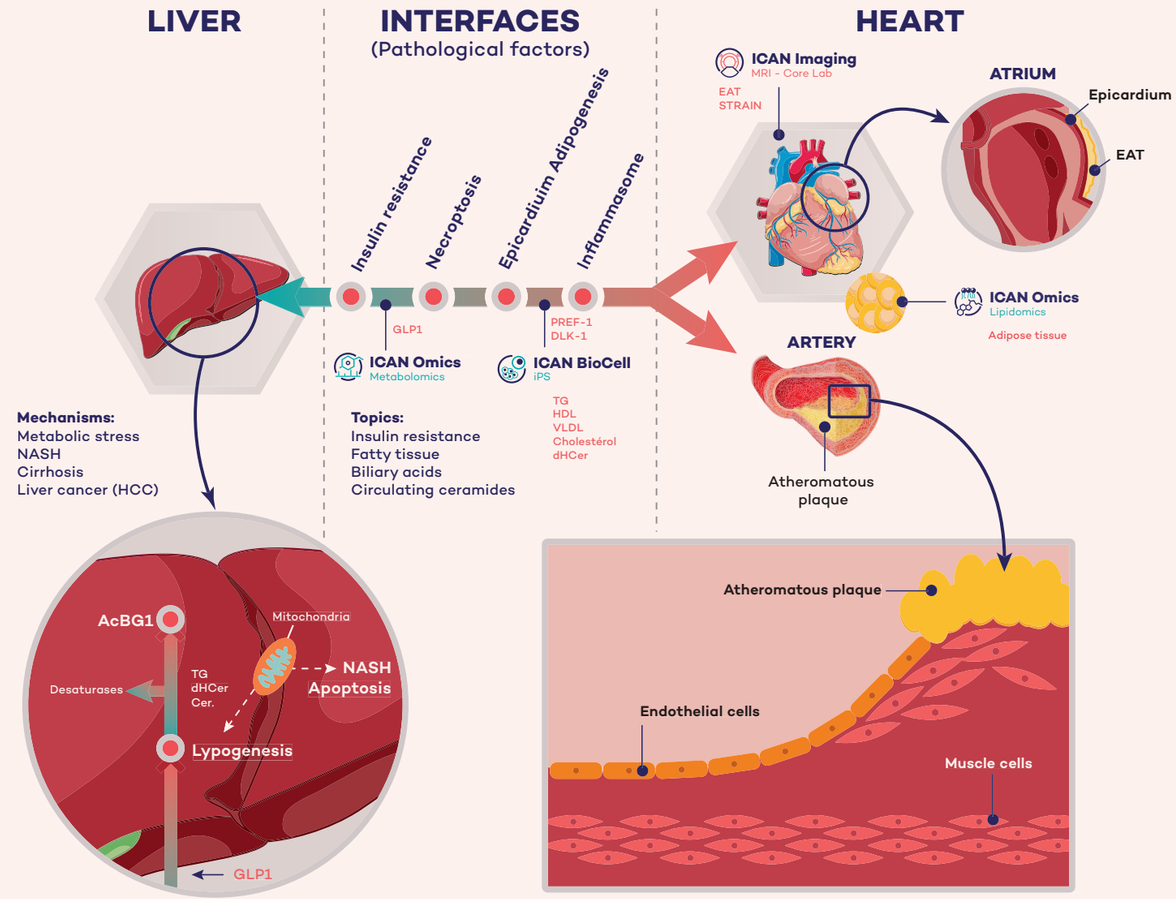
CROSSTALK BETWEEN THE HEART AND LIVER

On 30 November 2022, IHU ICAN invited the scientific community to a Heart/ Liver Workshop for a discussion of the latest advances in research on links between the heart, liver and blood vessels.

THIS EVENT WAS BASED AROUND 4 ROUND-TABLE DISCUSSIONS

- A link between the liver and heart: what clinical evidence?
- What are the biological bases for crosstalk between the liver, heart and blood vessels?
- How can new translational research on the liver, heart and blood vessels be implemented (cohort, imaging, biology)?
- How can a project be jointly developed at European level?

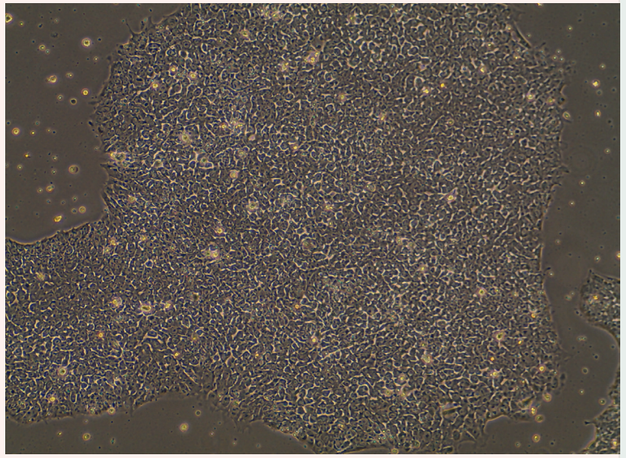
The event provided a forum for the 37 participants to discuss assumptions drawn from their respective fields of specialism, with a view to developing a major research project at European level as part of the renewal of the IHU.



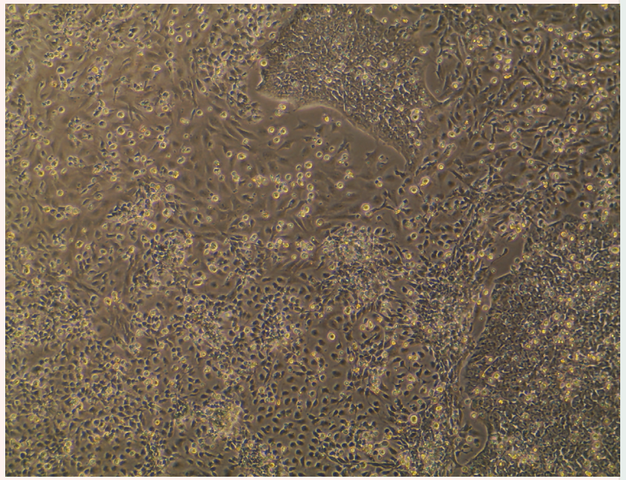
A NEW PATENT IN IHU ICAN'S PORTFOLIO

In December 2022, teams from IHU ICAN filed a new patent on a mechanism for stabilising iPS cells during reprogramming.

In the current climate of regulations and restrictions on animal testing and use of human embryonic cells, induced pluripotent stem cells (IPSCs) have a fundamental role to play. Using this technique, it is possible to create “cell models” *in vitro* from “simple” (adult) human somatic cells. These cell models are essential for understanding many diseases and testing the efficacy of potentially therapeutic molecules.
This patent is therefore fundamental, as the challenge lies in controlling the differentiation of these cells to create a stable *in vitro* “cell model”. It concerns an effective and reliable method to prevent “methylation” of parental genes (epigenetic) during the process, since a high level of methylation is harmful for cells. This patent is the result of a collaboration between IHU ICAN's iPS platform led by Vincent Fontaine (PhD) and Prof. Irène Netchine's Pathophysiology of Foetal Growth: IFG System and Parental Imprinting team, UMR 938 – Saint-Antoine Research Centre.



Cultured iPS cells in hypoxic conditions (required for maintaining balanced methylation)



Cultured iPS cells in normoxic conditions (normal conditions)

FLAGSHIP PROJECTS

BIG DATA AND COHORTS: A FUNDAMENTAL BASIS FOR INNOVATIVE RESEARCH PROJECTS

2023
- Big data and AI Conference
- ICONIC

2022
- EPOS-LT

2021
- Launch of MR004
  - LIVERBASE
  - DATABRAVE

2020
- Flagship MAESTRIA projects set up

2019
- Recruitment of 2 experienced data managers and creation of a research REDCAP
- eCRFs designed

2018
- 48 projects identified
- Regulatory support
- Creation of the cohorts catalogue
- Inventory of cohort projects
- Interviews with project leaders

2017
- Launch of a major cohort plan

2014
- 4 cohort projects launched (BARICAN, FIFA, Myocarde ICAN, APPROACH)

One of IHU ICAN's areas of expertise lies in structuring unique cohorts of patients with cardiometabolic diseases. These are designed not only to be scientifically relevant, but also to provide a robust basis from which to forge domestic and international academic and industry partnerships.

Since it was founded, ICAN has structured cohorts for clinical studies, and the IHU was quick to address the issue of big data in health and its use in research. Cohorts are a key biomedical research and value chain tool for a translational research institute like IHU ICAN. In order to be useful and valorisable, these cohorts must meet strict criteria in terms of regulatory compliance and the quality of data, phenotypes and samples or biological collections.

Through IHU ICAN's cohort plan introduced in 2017, it has been possible to inventory, structure and classify cohorts to create robust and secure databases from them. These cohorts now provide an invaluable basis for research, with over 42,000 patients included in cohorts, registries or clinical trials.

These cohorts are designed to anticipate translational research, the development of computerised solutions including AI, and computer-aided diagnosis, and to be reusable in subsequent partnerships.

IHU ICAN is thus developing a qualified and annotated range of high-value-added data enhancing the appeal of our research teams at global level. Combined access to large cohorts and ICAN's technological platforms provides fertile ground for companies seeking to establish proof of concept for their solutions.

COHORTS

FH-CALC cohort
(hypercholesterolaemia)
270 patients

SUPAT - PCV cohort
(cardiovascular prevention)
25,000 patients

METACARDIS cohort
800 patients
European extension
> 2,000 patients

FRAMES cohort
(metabolic steatosis)
600 patients
European extension
EpOS / Litmus
> 8,000 patients

National CARDIOGEN network
2,660 patients HCM = hypertrophic cardiomyopathies
3,210 patients DCM = dilated cardiomyopathies
1,000 patients ARVD= arrhythmogenic right ventricular dysplasia
ERN European extension

FASTRHAC cohort
(AF)
300 patients

LIVERBASE cohort
(Liver surgery)
2,000 patients

DATABRAVE Cohort
(Vascular surgery)
100 patients

ATLANTIS cohort
(TAVI)
1,500 patients

Transplant cohort
Heart and Liver
> 1,000 patients

OVER **42,000 INDIVIDUALS** INCLUDED IN COHORTS, **REGISTRIES** OR **CLINICAL TRIALS.**

Key

- Metabolic
- Cardiovascular
- Biocollection
- MRI CT Scan
- Ultrasound
- Nutrition
- Biopsies
- Optics
- Monitoring
- Longitudinal data
- ECG

CARDIOVASCULAR IMAGING AT THE HEART OF INNOVATION

ICONIC

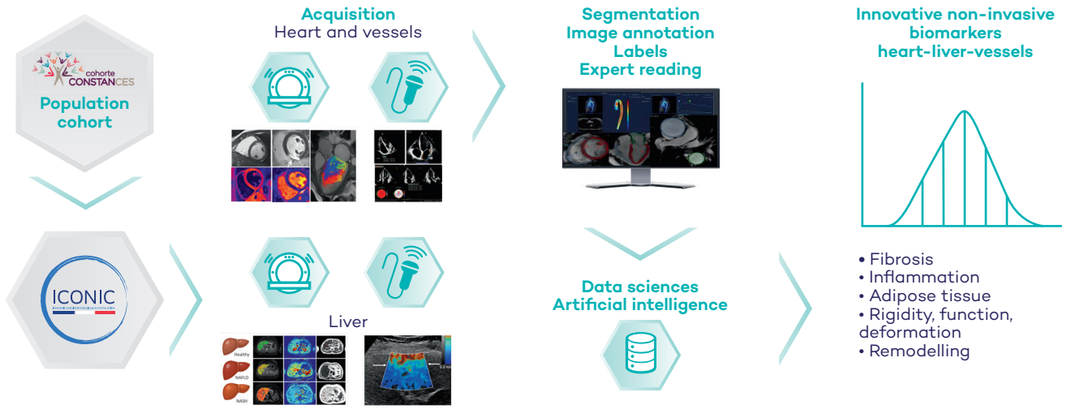
Cardiovascular diseases are the leading cause of mortality in Europe accounting for 32% of all deaths, far surpassing cancer.

Cardiology is a fast-moving field with the development of a new generation of custom implantable medical devices for individual patients (e.g.: prosthetic valves, circulatory support devices, etc.). Structural and functional multimodal imaging of the heart and aorta plays a key role in early detection and diagnosis of diseases, individualised risk assessment, and personalised treatment and care.

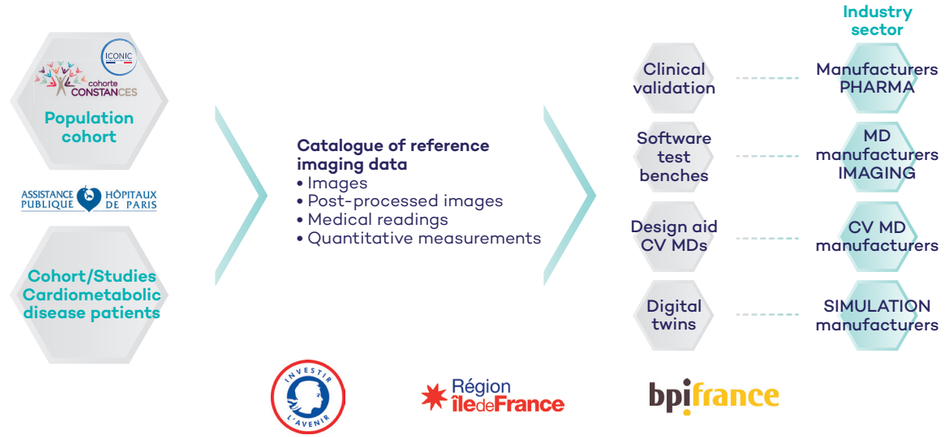
The prerequisites for using innovative new non-invasive imaging biomarkers are: access to the latest acquisition sequences, the creation of expansive catalogues of labelled and annotated raw images, and the development of new image post-processing software based on artificial intelligence.

Cardiovascular and metabolic imaging is now central to IHU ICAN's scientific and medical strategy, with the set-up of the ICONIC cardiometabolic population imaging project, which seeks to investigate 2,400 volunteers from INSERM's national epidemiological cohort, CONSTANCES, managed by Prof. Marie Zins. Two major grants were secured in 2022 and 2023: €1.5 M from the Ile-de-France region and Bpifrance to fund the development of a Sésame Filières project involving a heart-aorta imaging atlas and €1.2 M from the MSDAVENIR endowment to image young volunteers aged under 40. As a result, it will be possible to complete the ICONIC protocol, structure the equipment required for multi-modal cardiovascular and hepatic imaging, and recruit the first volunteers from the CONSTANCES cohort in late 2023.

OVERVIEW OF THE ICONIC PROJECT



The Sésame Filières project



The specific focus of the Sésame Filières project supported by the Ile-de-France region is to help industry players involved in medical imaging, the pharmaceutical industry, medical devices and digital simulation to devise new approaches to cardiovascular health. Through this sector, it will be possible to create a unique, partnership-based centre of excellence for the Ile-de-France region based on a structured and interoperable bank of labelled images, software and validated cardiovascular biomarkers, and offer advanced imaging including an anatomical, functional and haemodynamic assessment of the heart and aorta for the general population.

CARDIOVASCULAR IMAGING AT THE HEART OF INNOVATION

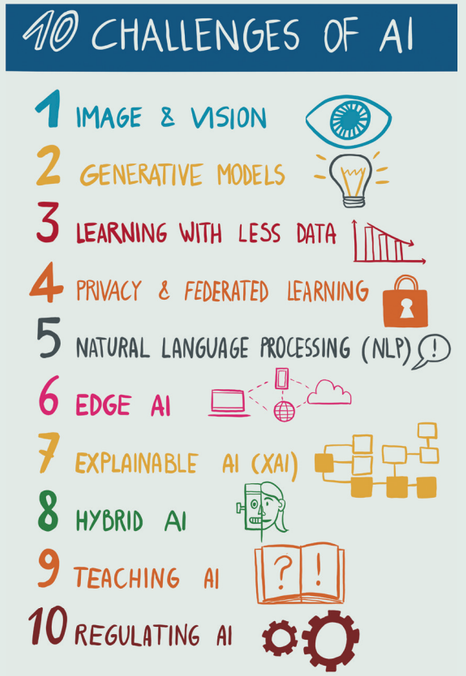
MAESTRIA

Atrial fibrillation (AF) is the most common heart arrhythmia and its incidence continues to rise as the population ages. It is one of the primary causes of embolic vascular events and heart failure, with 25% of strokes linked to AF. In most cases, AF is associated with a genuine myocardial disease, resulting in a hypertrophic, dystrophic and fibrous myocardium. In electrophysiological terms, cellular action potentials are short and there are numerous foci of abnormal automatism. This disease of the atrial myocardium precedes the onset of AF and is exacerbated by heart failure, arterial hypertension, valvular heart disease and ageing.

It is currently described as atrial cardiomyopathy. Recently, a link has been described between the abundance of epicardial adipose tissue (EAT) and risk of AF recurrence, providing further evidence of a relationship between AF and metabolic diseases such as diabetes and obesity. A source of free fatty acids and the principal energy substrate for the myocardium, EAT secretes numerous cytokines capable of regulating the extracellular matrix and myocardial inflammation or oxidative stress. Current methods of identifying this atrial cardiomyopathy, and thus patients at risk of AF, are highly inadequate. Imaging essentially involves measuring the size of the atria and assessing how effectively they are emptied, whereas the ability to visualise the myocardial structure, fibrosis, and adipose tissue infiltration or biological characteristics such as inflammation and oxidative stress is needed. Steps towards this goal have been made, with a major breakthrough revealing biological crosstalk between fat tissue (EAT) and the wall of the adjacent coronary artery, particularly affecting the vessel's oxidative stress regulation, combined with progress on EAT CT imaging, which is now able to provide data on its degree of inflammation or oxidative stress. Using machine learning, a “radiotranscriptomic” signature of coronary artery fat tissue has been established and validated as a biomarker of the severity of coronary heart disease. The team hopes it will be able to apply the same approach to diagnosing atrial cardiomyopathy by performing a similar analysis of synchronised heart CT scans of atrial EAT. The MAESTRIA (Machine Learning and Artificial Intelligence for Early detection of Stroke and Atrial Fibrillation) project launched in March 2021 seeks to develop and validate the first digital integrative diagnosis platform for atrial cardiomyopathy. Moreover, this project offers the first data hub dedicated to heart disease at European level, with potential for use in data science and artificial intelligence studies and research projects on heart imaging.

Below are some of the key steps taken through the MAESTRIA project:

- A workshop on health data and AI was held in Paris in June 2022
- The consortium's second general meeting took place in Maastricht in September 2022 with over 60 participants
- The consortium agreement was signed in November 2022



The project is split into eight work packages, from preliminary research to deployment of the applicable digital diagnostic platform, covering ethics, valorisation and network management.

ALL TEAMS INVOLVED IN THE MAESTRIA CONSORTIUM HAVE MADE GOOD PROGRESS THROUGHOUT 2022

Progress has been made on facilitating sharing of clinical and analysis data among partners enabling a link with the ORFAN international study led by the University of Oxford and Prof. Antoniades aimed at validating the “Atriomic Stroke” algorithm: the deep learning program for automated segmentation and radiomic analysis of the atria and periatrial tissue by CT scanning in collaboration with the Paris Public Hospital Network (AP-HP) health data warehouse team. An AI-based deep neural network for dynamic multimodal segmentation and atrial strain was also implemented, trained and validated, and 1,400 MRI cine loops of the heart and 2,100 cine loops in the short-axis view were collected and expertly annotated. A robust pseudonymisation tool is now available and can be used for the future prospective patient cohort with a view to validating biomarkers as part of a multimodal approach.

We should highlight the following achievements of Nadjia Kachenoura’s team at the Biomedical Imaging Laboratory (LIB) in collaboration with Prof. Ariel Cohen’s cardiology team at Saint-Antoine Hospital:

- Improvements to the Cardio-Track software (protected by Sorbonne University and ASN) allowing multi-chamber analysis of myocardial strain by feature tracking, providing fast and robust annotation of dynamic MRI images to supply AI algorithms.
- Collection and expert annotation of 1,400 MRI cine loops (56,000 images) of the heart in 4 and 2-chamber view and 2,100 cine loops (84,000 images) in the short-axis view. These data were acquired using different MRI machines (Philips, GE and Siemens) and MRI field strength of both 1.5 and 3T.
- Implementation, training and validation of a deep neural network (DNN) with complex attention points and sufficient image pre-processing to

Consortium General Meeting in Maastricht, 12 and 13 September 2022

improve the image quality, resulting in a specific network for short-axis images focused on the ventricles, which achieved a Dice coefficient of 0.92 and a specialised network for long-axis images, which achieved a Dice coefficient of 0.91.

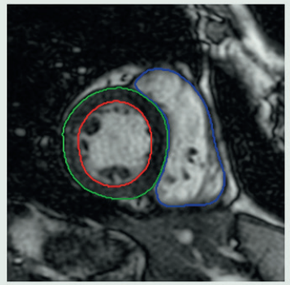
- The regulatory submission for the SAME study led by Dr Laurie Soulat-Dufour, in which Nadjia Kachenoura's team will create a tool allowing automated analysis of myocardial deformation of the heart chambers, originally developed for magnetic resonance imaging, to make it applicable to echocardiography. This transfer learning tool will be compared to manual segmentation of heart chambers. The acquisition and analysis of echocardiographic examinations is performed manually by cardiologist-echocardiographers. This new tool could be used to optimise the analysis time for these examinations.

OTHER MAJOR BREAKTHROUGHS HAVE ALSO BEEN ACHIEVED BY OTHER TEAMS IN THE CONSORTIUM

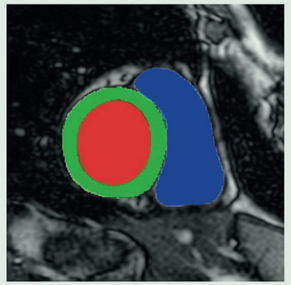
*Progress has been made on linking molecular mechanisms of atrial cardiomyopathy with electrophysiological anomalies through a detailed analysis of biological data from the Catch-ME cohort.

- The CATS AF prospective clinical trial led by Dr Nicolas Badenco, aimed at comparing electric intra-cardiac mapping with MRI imaging, has begun with the enrolment of the first de novo AF patients and the installation of an innovative ECG measuring device: the HRECG developed by the Dutch company YourRhythmics.
- Investigation of cell subsets involved in atrial cardiomyopathy has begun, using a single-cell transcriptomics approach and experimental atrial cardiomyopathy models (Boston-Paris collaboration). Using PET imaging, it is possible to analyse FFA storage specifically in the atrial openings, paving the way for investigating the impact of the metabolism on atrial functional properties. Epicardial adipose tissue is a source of inflammasome that could be a potential biomarker for atrial cardiomyopathy.

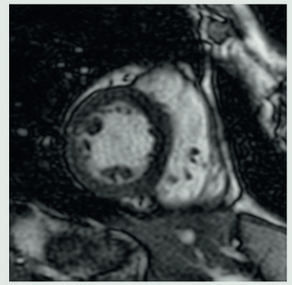
FULLY AUTOMATED AI-BASED SEGMENTATION OF THE HEART STRUCTURES



Final AI-based segmentation of heart structures



Ground truth mask AI-predicted mask (shades)



Native cardiac MRI image

Consortium General Meeting in Maastricht, 12 and 13 September 2022

METABOLIC LIVER DISEASES

EPoS Long Term

Non-alcoholic fatty liver disease (NAFLD) is considered to be the hepatic presentation of metabolic syndrome, and is now one of the most common causes of chronic liver disease. The actual prevalence of NAFLD is probably underestimated. Steatosis is visible on ultrasound in approximately 30% of individuals in the general population and approximately 8% have elevated transaminase levels.

The histological spectrum of NAFLD covers (a) isolated steatosis (non-alcoholic fatty liver, NAFL) (b) non-alcoholic steatohepatitis (NASH), which combines lobular inflammatory lesions and hepatocyte ballooning, (c) fibrosis and (d) cirrhosis.

Due to the ageing population and increasing prevalence of obesity and diabetes, the prevalence of severe forms of NAFLD is expected to rise with a significant impact on health spending.

Compared to other cancers, hepatocellular carcinoma (HCC) ranks sixth for incidence and fourth for mortality worldwide. It occurs in patients with chronic liver disease, mostly at the cirrhosis stage. The past twenty years have seen major epidemiological changes in the aetiologies of chronic liver disease. While viral infections have declined significantly, the prevalence of obesity, type 2 diabetes and metabolic syndrome has increased. Metabolic steatosis, which is the hepatic consequence of metabolic syndrome, has thus become the chief cause of chronic liver disease. Due to the constantly rising prevalence of obesity and diabetes, metabolic HCC has seen its incidence rise by 9% annually in the USA and is the highest climbing liver transplant indication. In contrast to other aetiologies, HHC may present without cirrhosis in subjects with metabolic steatohepatitis.

Given the increasing incidence of type 2 diabetes and obesity in western countries, the assessment of liver cancer risk in patients with metabolic syndrome has therefore become a major medical challenge.

However, uncertainties persist concerning the natural history and prognosis of NAFLD. In particular, these relate to patient stratification, since significant variability exists among individuals (particularly in terms of severity and the speed of disease progression, cases of regression, etc.), prognosis of progression, development into cancer, the role of comorbidities or complications, and the impact of therapeutic intervention (medication or surgery) on the course of the disease. With several drugs under development for NASH, it is now essential that we understand the natural history of the disease.

- **The key medical and scientific issues are as follows:**

(1) Which patients are at risk of disease progression?
(2) When diagnosed early (early-stage fibrosis), which patients will progress quickly?
(3) What is the incidence of complications in the absence of treatment?
(4) Which patients respond to treatment including surgery?
(5) Will mortality linked to hepatic complications of NASH become the chief cause of mortality in some patients given the progress made in primary cardiovascular prevention?

These key topics are addressed by identifying and validating non-invasive markers that can be used to select candidates for treatment and trace the course of the disease (progression or regression) within EpOS-LT, a retrospective and prospective cohort of well-characterised patients monitored by Prof. Vlad Ratziu in the gastroenterology department of the Pitié-Salpêtrière hospital group covering the full severity spectrum of NAFLD.

IHU ICAN created the cohort for a study that is compliant with research methodology MR-004.

ICAN Lipidomics

This research relates to the secondary reuse and analysis of data and samples collected during the routine treatment and care of patients seen in consultation and/or hospitalised or acquired in connection with another completed study. The analyses will focus on stratifying the risk of NAFLD progression by modelling the simultaneous longitudinal evolution of three non-invasive tests related to the liver biopsy (which continues to be the gold standard for assessing fibrosis) to determine disease progression or regression thresholds and develop a patient follow-up tool based on a digital twin model through the sub-studies NIT-MOOD and ANNITIA.

The analyses will also involve the most appropriate artificial intelligence tools for integrating complex heterogeneous data (including imaging and omics), which will improve interpretation of biopsies that are currently subject not only to variability in terms of sampling and among observers, but also to a purely qualitative or semi-quantitative assessment of lesions of interest (inflammation, fibrosis).

NASH clinic – unique treatment and care for NASH in France

IHU ICAN teams have joined forces with the Paris Public Hospital Network (AP-HP) to found the NASH clinic, a unique day unit designed to improve the everyday treatment and care of NAFLD patients.

The NASH clinic is France's first multidisciplinary hospital facility for the diagnosis, care and treatment of patients with metabolic steatosis. It has already benefited nearly 350 patients since it was opened. The NASH clinic seeks to anticipate and pre-empt NASH complications (early atherosclerosis, arterial hypertension, diabetes, etc.) and offer personalised care to all patients, taking account of their clinical phenotype, personal history and environment to ensure optimal compliance with medical guidelines. Patients follow a simplified and unified pathway involving day hospitalisation in Pitié-Salpêtrière hospital's hepatogastroenterology and nutrition departments. Medical specialists, including hepatologists, radiologists, cardiologists, dieticians, diabetologists and surgeons, all work within the same time period to perform the necessary examinations to establish a phenotype and accurate diagnosis with an assessment of hepatic and cardiometabolic risk. To enhance the support offered to patients, the programme also includes a therapeutic education consultation, which is essential for improving compliance with therapy plans put forward.

Therapeutic education is one of the cornerstones of the NASH clinic. It provides patients with information on the disease and contextualises the disease, the required approach, and steps to be taken by and on behalf of the patient, in a way that is tailored to them. Such support is essential for prompting a behavioural shift with regard to health, thus creating the necessary conditions for effective treatment and care.
Before each therapeutic education session, a questionnaire is completed to assess patients' knowledge of NASH and the associated risk factors. The results show that patients are very poorly informed of the disease, since over half are unfamiliar with NAFLD/NASH, its associated risk factors, and its potential to develop into cirrhosis. However, we have also observed that most patients are concerned or even very concerned about their disease potentially progressing.
Thanks to the NASH clinic, it is therefore possible to identify severe forms of liver disease more effectively, explore comorbidities associated with metabolic steatosis (screening for cardiovascular (CV) risk), offer therapeutic education sessions, provide advice on diet and appropriate physical activity, and offer patients a personalised pathway with overall stratification of their hepatic, metabolic, and cardiovascular risk.

FOCUS ON 3 BENEFITS OF THE NASH CLINIC

Weight:
35% of patients have lost 5% of their initial weight and 11% have lost 10%. The proportion of patients who lost 5% of their initial weight was significantly higher in the group that attended therapeutic education sessions, emphasising the key role played by therapeutic education.

Cardiovascular risk and primary prevention strategies:
Among patients with no known coronary heart disease: 30% of patients had high to very high CV risk (with a calcium score* of 100).
This figure highlights the importance of the NASH clinic which takes account of extra-hepatic risk factors.

Therapeutic education: assessing patients' knowledge of the disease and its risk factors
Overall, patients are very poorly informed of the disease, with over half unfamiliar with NAFLD and its risk factors. However, despite their lack of knowledge, 50% are very concerned. Therapeutic education and transfer of knowledge of the disease and its risk factors correlate with improved patient compliance with therapeutic guidelines, reflected in higher weight loss observed in the Therapeutic Education group.

***Calcium score:** the coronary artery calcium score is an assessment of the spread of calcified atherosclerotic plaque deposits in the coronary arteries. It is calculated based on a CT chest scan.

EXTREME PHENOTYPES

What is familial hypercholesterolaemia (FH)?

Familial hypercholesterolaemia or FH is a disease characterised by high LDL or "bad" cholesterol levels from birth.
This form of hypercholesterolaemia is a hereditary familial disease of genetic origin that is not caused by poor lifestyle or diet.
The disease is "dominant inherited", which means that just one of the two copies of each gene (one inherited from each parent), needs to be defective in order for the disease to present. There are two forms of familial hypercholesterolaemia:

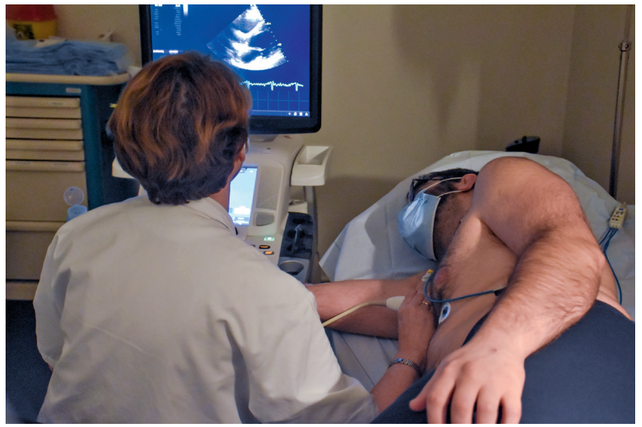
- A homozygous form linked to LDL cholesterol 6 to 8 times higher than normal levels (between 6g/l and 12g/l). This rare form is thought to affect 1 in 300,000 people.
- A heterozygous form linked to LDL cholesterol at least twice as high as normal levels (between 1.9g/l and 4g/l). 1 in 250 people is thought to suffer from this form, which equates to almost 300,000 people in France.

These abnormally high levels of LDL cholesterol are due to poor elimination. This "bad cholesterol" can accumulate in:

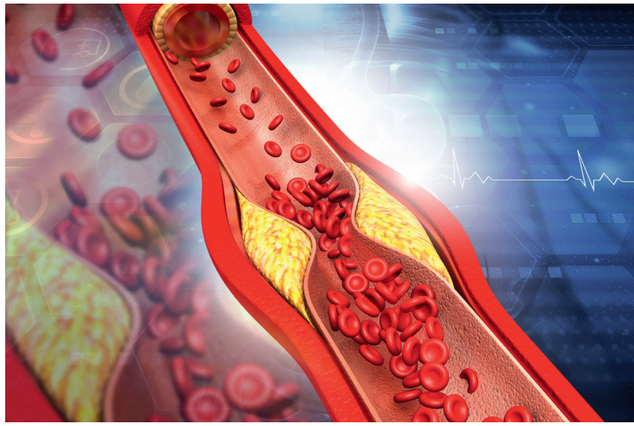
- the arteries which, from childhood, promotes atherosclerotic progression, causing often premature cardiovascular complications (before the age of 20 in homozygous patients and before 50-60 in heterozygous patients).
- the skin, extensor tendons of the hand or Achilles tendons (xanthoma) and eyelids (xanthelasma) in the form of yellowish nodules or blotches.
- the eyes, forming a whitish ring around the irises (arcus senilis or gerontoxon).

This is an invisible disease, since over 90% of sufferers in France are not currently diagnosed.

Failure to provide screening and early treatment and care leads to an elevated risk of cardiocvascular events even in very young subjects. Learned societies concur on the principle that individuals with familial hypercholesterolaemia are at high cardiovascular risk from the outset.



Transthoracic echocardiography (TTE)



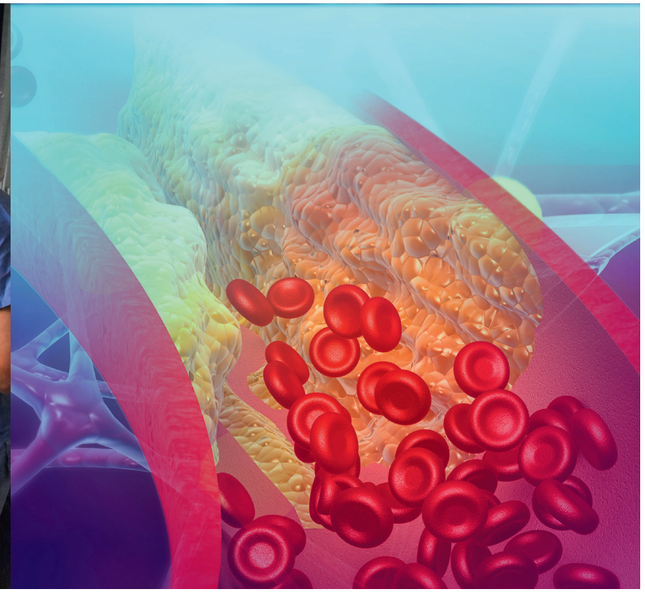
Cholesterol plaque formation

Familial hypercholesterolaemia: complications that should not be neglected

Homozygous familial hypercholesterolaemia can lead to very serious cardiovascular complications, including myocardial infarction and premature sudden death before the age of 30 or in childhood if left untreated.
Heterozygous familial hypercholesterolaemia is also a serious illness that can lead to cardiovascular events in approximately 50% of men under the age of 50 and 30% of women under the age of 60. Such events may occur from the age of 20 if the disease is left untreated. Without treatment, the condition of 40-year-old familial hypercholesterolaemia patients' arteries is similar to that of individuals aged 80.

Patients with familial hypercholesterolaemia have an elevated risk of coronary heart disease. There is a direct link between LDL-C levels and the risk of cardiovascular events (CVEs), as demonstrated by numerous epidemiological, genetic and intervention studies with statins. However, familial hypercholesterolaemia is associated with inter-individual variability, and therefore screening for vascular disease by imaging is worthwhile to establish a personalised therapeutic algorithm. The coronary artery calcium score (CAC score) is increasingly used in France to reclassify patients in terms of cardiovascular risk. Several meta-analyses have shown that a score of zero indicates a very low risk of events, regardless of the number of risk factors present. The calcium score has been fully assessed for heterozygous familial hypercholesterolaemia, revealing that approximately 45% of subjects do not exhibit calcification. In contrast, if the CAC score exceeds zero, it is possible to predict the risk of cardiovascular events during follow-up and restratify the risk of asymptomatic subjects. However, links have been established between hypercholesterolaemia and calcification: supra-aortic calcified masses in homozygous FH patients and premature calcification in connection with chronic exposure to high LDL-C (cholesterol burden) equivalent to cigarette "packet-years" and the calcifying role of statins. Determinants for the presence/absence of calcification in this population are not currently known.
Two other extremely pro-atherogenic types of lipoproteins can considerably increase cardiovascular risk in these patients: lipoprotein (a) [Lp(a)] and triglyceride-rich lipoproteins (TRLs). The atherogenicity of Lp(a) can mainly be ascribed to the fact that it transports oxidised phospholipids and its apolipoprotein (a) has prothrombotic and antifibrinolytic properties. Statins do not reduce Lp(a). TRLs are highly atherogenic and contribute to residual risk, since their cholesterol is not taken into account in standard lipid profiles. TRLs contain an apolipoprotein B (apoB) and apolipoprotein E (apoE) molecule, which ensures they are recognised by the hepatic receptors ensuring their purification.

LDL - Apheresis



Cholesterol deposits

Research to improve understanding of familial hypercholesterolaemia

◦ FH CALC

The main objective of this study led by Dr Antonio Gallo, for which 268 heterozygous familial hypercholesterolaemia patients have been recruited, is to assess the prevalence of high coronary artery calcium (> 75th percentile of the MESA reference population) using cardiac CT scanning and, among patients not exhibiting calcification, estimate the prevalence of non-calcified plaque. Highly advanced imaging-based and biological phenotyping was applied to this cohort, with precise phenotyping of the lipoprotein profile including apolipoproteins (a), B100, C2 and C3, apo E polymorphism and apo(a) size, as well as ceramide and phospholipid levels, which were performed to investigate their role in calcified/non-calcified vascular disease due to coronary, carotid and femoral artery atherosclerosis, and thus isolate the contribution of each apo to subclinical vascular disease.

It is anticipated that residual risk is associated with high Lp(a) and TRL levels despite optimal hypolipidemic treatment. Links between apo(a) size, apoE polymorphism, apoC3 concentrations and cardiovascular risk could be used to develop a calcified/non-calcified vascular disease prediction score in order to tailor therapeutic strategy to each patient's individual needs. An understanding of links between LDL-C, Lp(a), TRLs and associated apolipoproteins should provide the scientific foundations for developing novel therapeutic strategies targeting the expression of these new biomarkers. Statistical analyses are currently in progress.

◦ CARDIOMET

As part of the European Metrology Programme for Innovation and Research (EMPIR), the EURAMET project sought to assess the accuracy of conventional biomarkers for evaluating cardiovascular disease risk. Current treatment and care of dyslipidaemia in patients with atherosclerotic cardiovascular disease (ASCVD) is based on traditional serum lipids. Reliable and comparable measurements of blood lipids are therefore essential for predicting cardiovascular risk and providing patients with appropriate treatment. To ensure that clinical measurements are comparable between different methods, locations and times, it is essential to provide traceable measurement results on an accurate basis. An in-depth, independent assessment is required to demonstrate that the analytical performance of a standardised laboratory test meets relevant analytical performance targets. As well as assessing the causes of tests' inaccuracy, it is also very important to evaluate whether analytical performance targets are appropriate. The project has helped evaluate the relevance of current performance criteria for conventional test methods and propose new approaches to improve the accuracy and reliability of measurements that support the latest clinical practice guidelines.

Various approaches were assessed with a view to modifying current criteria and developing approaches aimed at i) maintaining analytical performance when lipid levels are high, ii) improving accuracy and reliability when lipid levels are low and iii) addressing variability linked to sample-specific factors.

While reference measurement systems are available for lipids, reference standards for advanced lipoprotein tests either do not exist or could be improved. The project has contributed to the development of traceability chains aimed at standardising advanced lipoprotein test methods that could be used to reduce undiagnosed cardiovascular risk.

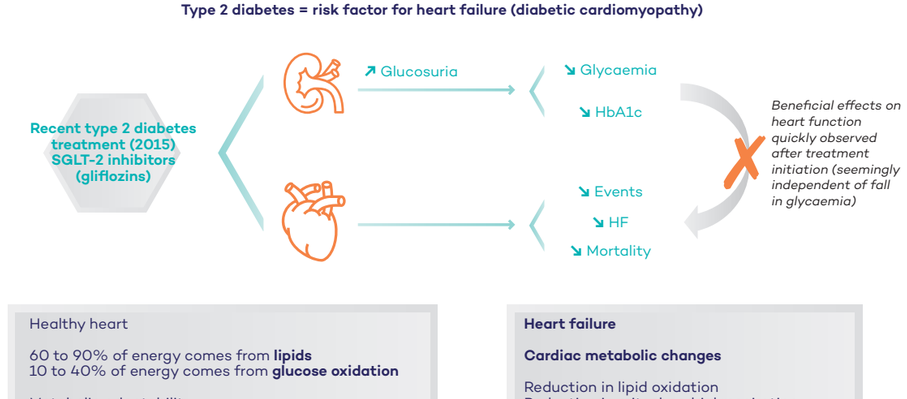
The main objective of the CARDIOMET clinical study led by Dr Antonio Gallo was to compare the apolipoprotein profile of patients with familial hypercholesterolaemia (FH), a common genetic disorder linked to an increase in LDL-C levels and elevated cardiovascular risk, by comparing subjects with concomitant hypertriglyceridaemia (hyperTG) to those with isolated hypercholesterolaemia. Its secondary objectives were to compare the subclinical deficiency of FH patients with and without hyperTG as a measurement of coronary artery atherosclerotic load (coronary artery calcium – CAC), carotid artery atherosclerotic load (ultrasound) and femoral artery atherosclerotic load (ultrasound).

98 subjects with a molecular or clinical diagnosis of familial hypercholesterolaemia were recruited and stratified by the presence/absence of hyperTG, defined as TG 135-500 mg/dL, in a prospective observational case-control study. The exclusion criteria for the study were: severe hyperTG (> 500 mg/dL), statin intolerance, pregnancy, uncontrolled diabetes (HbA1c >10%), and use of treatments for human immunodeficiency virus or corticosteroids.

A preliminary analysis was performed on 46 samples to select the investigation population and harness the added value of apolipoprotein profiling to predict the presence of atherosclerotic cardiovascular disease (defined as the presence of CAC) in addition to standard lipid biomarkers. 46 subjects were selected and pair-matched for triglyceride levels and stratified by the presence or absence of CAC (CAC+ and CAC- groups). Apolipoproteins (a), A-1, A-II, A-IV, B-100, C-I, C-II, C-III and E were measured using a reference method based on liquid chromatography-isotope dilution mass spectrometry (LC-IDMS) developed by Leiden University Medical Centre (LUMC) in the Netherlands. No significant difference in apolipoprotein concentrations was observed between the two study groups after age adjustment. Correlations within the standard lipid biomarkers and apolipoproteins were subsequently explored in the two groups. It was observed that ApoB and E were only correlated with TG levels in the CAC+ group, while Apo A-IV, Apo C-II and Apo C-III were more strongly associated with the presence of CAC, although a significantly weaker correlation was also established in the CAC- group. These preliminary results suggest that some apolipoproteins could play a specific role in predicting the atherosclerotic process in FH in addition to standard lipid biomarkers.

This study showed that measuring apolipoprotein by mass spectrometry was possible for a moderately large cohort (<100 patients). Although this method could certainly be used for large cohorts, it is clear that fully automated immunoassays would significantly speed up the process and reduce costs, provided that the results were accurate. Consequently, the reference method based on IDMS will play a critical role in standardising immunological assays: the results of standardised apolipoprotein tests that are traceable by IT will enable clinical studies to be conducted on very large cohorts and data from several studies to be aggregated, even if different immunological assays have been used.

CROSSTALK
DIABETES AND CARDIOVASCULAR DISEASES



Organ crosstalk: a new key research area

Epicardial adipose tissue forms an interface between metabolic diseases, in particular diabetes, and cardiovascular diseases, and appears to play a fundamental role in the pathophysiology of myocardial dysfunction. In recent years, clinical studies on new type 2 diabetes (T2D) treatments, GLP-1 agonists and SGLT2 inhibitors, have demonstrated major cardiovascular benefits in terms of significantly reducing cardiovascular events, which go way beyond their direct impact on glycaemic control.

Moreover, the ability to make alternate use of glucose and lipids depending on myocardial requirements is a key characteristic of heart muscle physiology. After a large meal containing glucose, more pyruvate and lactate are used. During periods of famine, more fat is used. The proportion of anaerobic metabolism increases during periods of hypoxaemia. Ketone bodies only play an important role as substrates for cardiac metabolism in cases of advanced heart failure. Increased availability of triglycerides (TGs) and non-esterified fatty acids (NEFAs), as observed in type 2 diabetes, is linked to impaired heart function in rodents and humans. In cases of lipotoxicity, less glucose is absorbed by the heart and lipids are the main substrate for synthesising adenosine triphosphate (ATP). Compared to healthy subjects, more fat is used in the hearts of untreated diabetic patients.

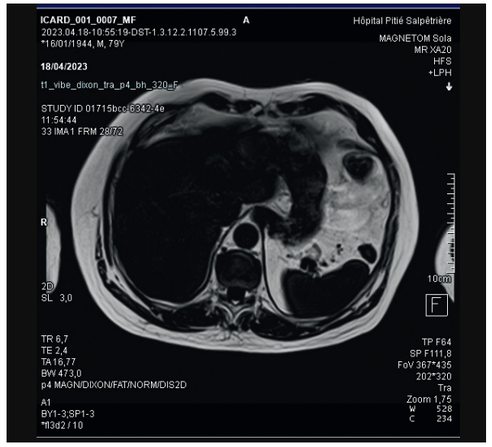
The heart's versatility in terms of using metabolic substrates is referred to as “metabolic flexibility”. Reduced versatility in terms of the heart's substrate use, as observed in T2D, is known as “metabolic inflexibility”.

Chronic hyperglycaemia and/or lipid imbalance impair fuel use in the heart and increase some T2D patients' risk of developing heart failure (HF). Their treatment and care could be adjusted if myocardial dysfunction linked to metabolic inflexibility is detected early. The need to discover non-invasive markers of cardiometabolic disorders represents a major challenge. Moreover, since substrate use is essential for cardiac contractility, optimising substrate oxidation can rapidly improve heart function and reduce adverse effects such as hospitalisation for heart failure and all-cause mortality in the short term. Promotion of the metabolic switch may explain clinical consequences observed in clinical trials with gliflozins.

ICARD

Three major trials have demonstrated that SGLT2 inhibitors prevent heart failure in patients with type 2 diabetes and atherosclerosis. Moreover, the recent DAPA-HF trial shows that dapagliflozin improves mortality and reduces hospitalisations for heart failure in heart failure patients with reduced ejection fraction who are receiving optimal medical treatment. It is interesting to note that the magnitude of these effects was similar in diabetic and non-diabetic patients. However, the mechanisms underpinning these beneficial effects are, as yet, hypothetical. There is therefore a need to better understand the mechanisms of action of SGLT2 inhibitors and dapagliflozin in particular.

Several mechanisms of action have been suggested, the first of which relates to its diuretic and natriuretic effects which may contribute to improving haemodynamics by reducing blood volume. Another theory is that an improvement in myocardial energy supply and metabolic efficiency may be induced by an increase in ketone bodies or erythropoietin. Other effects have also been observed, including improved arterial rigidity, vascular resistance and myocardial fibrosis and reduced visceral and epicardial adipose tissue and hepatic steatosis. Several studies have reported a reduction in left ventricular (LV) mass and an improvement in LV diastolic function based on echocardiography, although most of these studies targeted type 2 diabetes patients without heart failure. The randomised, controlled EMPA-HEART study using MRI confirmed that empagliflozin reduces left ventricular mass in type 2 diabetes patients and in cardiovascular disease. Other MRI studies involving heart failure patients are in progress.



ICARD study

The main objective of the ICARD study led by Prof. Alban Redheuil and funded by AstraZeneca is to use MRI to assess changes in the left ventricular (LV) extracellular mass index (ECMI) induced by 10mg of dapagliflozin administered once a day for 6 months in 40 heart failure patients with reduced ejection fraction. Additional analyses will be performed to describe the magnitude and relationships between changes in tissue characteristics (dense interstitial fibrosis and fat) from multiple organs (heart, liver, abdominal adipose tissue) while administering dapagliflozin. The first 3 patients were enrolled in late 2022.

Cardiology consultation with Prof. Isnard

MET-INF-T2D - Metabolic inflexibility of the heart as a predictive factor for the onset of heart failure in patients with type 2 diabetes

Within the type 2 diabetes population, it is difficult to identify patients with myocardial metabolic inflexibility. However, these patients are at particularly high risk of developing early heart failure. Finding markers to identify these at-risk subjects is therefore a major scientific objective in efforts to prevent/delay the onset of heart failure. Insulin therapy is initiated if oral hypoglycaemic agents combined with GLP-1 therapy fail to control HbA1c levels. After 5 days in hospital, T2D patients continue their insulin therapy at home. After 15 days, glucose levels are significantly reduced, requiring metabolic adaptation by means of an unknown mechanism. Patients presenting with cardiac metabolic inflexibility will be identified during admissions for insulin therapy.
The main objective of the MET-INF-T2D study led by Prof. Fabrizio Andreelli and funded by the Fondation de France, Fondation de l'Avenir and Entrepreneurs and Go federation is to identify at-risk subjects defined by the existence of impaired maximum longitudinal contractility of the left ventricle based on a magnetic resonance imaging (MRI) measurement of myocardial deformation before and after an imposed metabolic change (insulin treatment and correction of hyperglycaemia) within a population of type 2 diabetics in primary prevention requiring the initiation of insulin therapy due to uncontrolled diabetes (HbA1c of 10%).
The inability to modify fuel oxidation when reducing glucose levels through insulin therapy is thought to result in subtle changes in ultrastructure, heart function and myocardial microcirculation in patients with metabolic inflexibility. MRI allows a non-invasive, multidimensional approach to diabetic cardiomyopathy by providing quantitative structural and functional data and tissue characterisation at tissue level *in vivo*. The aim is to recruit 30 patients and 20 healthy control subjects.

INTERNATIONAL PROJECTS

NON-ALCOHOLIC FATTY LIVER DISEASE

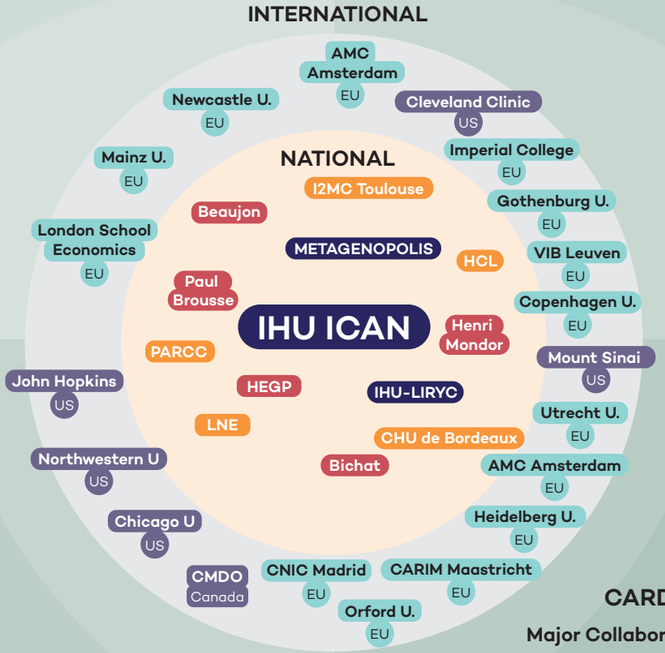
Major Collaborative projects

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



CARDIOMETABOLIC BIOMARKERS

Major Collaborative projects

PSPC PACIFIC
RHU CHOPIN
ISR FH CALC
International Lab (Johns Hopkins)
EMPIR CARDIOMET
ISR ICARD

CARDIOPATHIES

Major Collaborative projects

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

Investment for the future · Europe · AP-HP · North America · National

CARDIO-METABOLISM

TRAINING IN

A PRACTICAL APPROACH TO TRAINING

Sharing and disseminating knowledge, both with the scientific and medical community and the public, forms an integral part of IHU-ICAN's remit. To achieve this, IHU-ICAN applies highly practical tools to share innovations it helps develop with the widest possible audience and works with first-class partners.

JUNIOR LIVING LAB

IHU ICAN works with engineering students at POLYTECH Sorbonne on their internship project. Their task is to propose solutions to medical challenges encountered in everyday practice by clinicians in the IHU community.
In 2022, students embarked on the Uthop'IA project, which will take them several years to complete.
The project involves a humanoid robot delivering digital therapeutic education to heart failure patients.
Following work carried out by students at the ECE engineering school in 2021, a patient interface was developed in 2022 offering a fun user experience. Since heart failure patients tend to be old and very tired, they need tools that are easy to use to increase their chances of compliance and help them understand the information provided. In tandem with this work, a group of POLYTECH students conducted a robotics project aimed at teaching a robotic device to move around in a hospital setting. The robot needs to detect and avoid obstacles. It also needs to recognise a route from point A (its charging station) to point B (a patient's room). A second group focused on the engineering task of teaching the robot to open the door to a patient's room. The movement and door opening stages were two very complex steps in the project. Students had to harness all their creativity and engineering skills to complete these tasks.
The third group worked on another component of the Uthop'IA programme, which involved patients returning home for remote follow-up. They worked on medical telesurveillance projects.

Master's Degree in Extracorporeal Circulation and Circulatory Support

Autumn 2022 saw the graduation ceremony for the first class of students completing the master's degree in ECC put together by experts in extracorporeal blood circulation from the IHU ICAN community. This year's participants were student nurses from heart surgery suites across France. The master's degree, whose ultimate aim is to gain recognition for the role of perfusionist as a profession in its own right, is supported by IHU ICAN. As well as providing content for TU 13: Research Methodology, ICAN supports 3 interns with methodology and completing their internship.

Monthly scientific seminars informing the scientific and medical community of the latest innovations in cardiometabolism

In collaboration with UMR 1166, IHU ICAN holds monthly face-to-face or remote scientific seminars to train and brief its scientific and medical community in the latest innovations and practices in the field of cardiometabolism. Each expert invited by a member of the ICAN community gives a talk on a cutting-edge research topic.

JANUARY	Liver-on-a-chip and 3D models	**Cécile Legallais** Head of the Biomechanical and Bioengineering Laboratory – Compiègne University of Technology
FEBRUARY	Ultrafast ultrasound and its applications	**Mathieu Pernot** Physics for Medicine Laboratory – ESPCI Paris – Pitié-Salpêtrière Hospital
MARCH	Genetics and single-cell sequencing to identify novel therapeutic targets for cardiovascular diseases	**Patrick T. Ellinor** Member of the Broad Institute, Harvard – Director of the Cardiac Arrhythmia Service, Massachusetts General Hospital – Professor of Medicine, Harvard School of Medicine
APRIL	Seipin deficiency as a model for adipocyte dysfunction	**Xavier Prieur** Thorax Institute, Team 4, Cardiometabolic diseases – University of Nantes
MAY	Resolving spatial heterogeneity using NanoString's high-precision and single-cell profiling platforms	**Jean-Baptiste Pénigault** – PhD – NanoString
SEPTEMBER	Extra-hepatic functions of PCSK9 & Identifying a gain-of-function LIPC variant	**Cédric Lemay** Director of Research – Thorax Institute – Team 4 Cardiometabolic Diseases – University of Nantes
OCTOBER	Arrhythmogenic right ventricular cardiomyopathies: from animal models to innovative approaches	**Jérôme Montnach** CNRS Research Fellow – Thorax Institute – University of Nantes
NOVEMBER	Exploring the role of standard and non-standard biomarkers in the context of atherosclerotic load	**Chiara Macchi** Research Fellow – Department of Pharmacology and Molecular Biology – University of Milan

A PRACTICAL APPROACH TO TRAINING

IHU ICAN Young Researchers Summer Training and CMDO Boot Camp

In 2022, IHU ICAN staged its first Young Researchers Summer Training event.

This involved hosting 5 students from the Cardiometabolic Health, Diabetes and Obesity Research Network (CMDO) in Quebec, a long-standing ICAN partner. Under the new format, PhD students and post-doctoral fellows from the ICAN community and CMDO took part in a tour in which they discovered or developed their knowledge of ICAN scientific platforms, attended careers workshops to prepare young researchers for future job interviews, and found out about all the opportunities available to qualified researchers. The interns also attended classes on sarcopenic obesity and treatment and care of NASH patients through the NASH clinic, a unique multidisciplinary programme put together by IHU ICAN teams.

This new format, which proved a hit among students, will be further enhanced in 2023.

In May 2022, young French researchers attended the CMDO winter camp, which had been postponed to spring due to the pandemic.

SPONSORSHIPS

SPONSORSHIP SUPPORTING INNOVATION

In January 2021, IHU ICAN's management started developing a sponsorship policy to support cardiometabolism projects run by the IHU's doctors and researchers. Sponsorship is a key financial tool for conducting innovative projects that cannot initially be publicly funded.

While cardiometabolic diseases are chronic conditions seriously affecting the lives of millions of patients, there is little public awareness of the challenges and consequences they entail, which means they often fall below the radar of potential sponsors. It is essential to explain the challenges faced by doctors and researchers when seeking to improve patients' everyday lives and further understanding of metabolic diseases' pathophysiological mechanisms. Diabetes, obesity, NASH and cardiovascular diseases interact with each other and therefore require multidisciplinary research.

ICAN is a hub of medical and scientific expertise focused on major projects whose purpose is to elucidate how organs interact and influence each other and shed light on the origins and progression of metabolic diseases, with a view to developing precision cardiometabolic medicine.

To fulfil its remit, ICAN forges academic and industry partnerships and works with leading teams. However, the IHU also needs support from sponsors to achieve further innovation, conduct projects and pilot studies, establish proof of concept, and save time on funding applications.

Donations are used to develop future programmes in the following key areas:

- Imaging to identify new biomarkers for metabolic diseases and thus improve prevention, diagnosis and treatment efficacy monitoring
- Data, AI and cohorts to develop robust, collaborative and innovative research programmes that are compliant with regulations
- Biology of cardiometabolic diseases, new interfaces: microbiota, fatty tissue, cholesterol and liver, to understand the mechanisms of cardiometabolic disease development and progression
- Rare diseases: improving understanding of extreme and rare phenotypes.

Further information on IHU ICAN's sponsorship policy can be found at:
www.ihuican.org

In 2022, IHU ICAN raised €591,000 thanks to the generosity of committed sponsors.

We would like to thank all new partners who have joined IHU ICAN's community of sponsors:

- ABBOTT
- ADICARE
- ASTRAZENECA
- CARREFOUR FOUNDATION
- FONDATION CONSTANCE ET ANDREI RHOE hosted by the Fondation de France
- FONDATION CREDIT AGRICOLE IDF MECENAT
- FRENCH FEDERATION OF CARDIOLOGY
- VIOT CONSULTING

We would also like to thank the following sponsors for their continued support and commitment:

- BIOTRONIK
- BOSTON SCIENTIFIC
- ENTREPRENEURS AND GO
- Mrs FOTIADI
- LIGUE CONTRE LES CARDIOMYOPATHIES
- MEDTRONIC
- MICROPORT

DONATIONS ARE VITAL!

A NEW STRATEGY SUPPORTING SCIENTIFIC PROJECTS

2022 Heroes' Race

For the first time, on 19 June 2022, IHU ICAN took part in the Heroes' Race, a charity event aimed at raising funds for a specific project. A total of €5,865 was raised. This money will help improve the treatment and care of heart failure patients by directly contributing to the UTHop'IA/RobEduc project. The donations have been used to fund the engineering phase enabling the robot's movement.

We would like to thank all participants and donors.

Visit from Crédit Agricole Ile-de-France Mécénat

Crédit Agricole IDF Mécénat supported IHU ICAN research teams through its contribution to the ARVC (Arrhythmogenic Right Ventricular Cardiomyopathy) research project. As part of this collaboration, we were pleased to host a visit from their delegation, who attended the project presentation delivered by the dedicated research team consisting of Prof. Estelle Gandjbakhch (Head of the Rhythmology Unit), Eric Villard (Scientific Head of Team 1 UMRS 1166) and Pierre Bobin (Postdoctoral fellow). The visitors were also shown the research laboratories of UMRS 1166 and the cell culture box used to develop engineered heart tissue (EHT), a model that is currently unique in France. (Photos ©Alkama)

THE FONDATION CONSTANCE AND ANDREI RHOE AND IHU ICAN

Constance and Andrei Rhoe

Both born and educated in Romania (with MScs in Chemical Engineering), Constance and Andrei Rhoe led successful careers in which their scientific training in Romania played a key role. They settled in France over 40 years ago and were high achievers in their field.
In 2015, they decided to fund a foundation, which was named the Fondation Constance et Andrei Rhoe under the aegis of the Fondation de France. Two key areas of action define the goals of this foundation:
1. Medical research
2. Musical education and awareness-raising on democracy and citizenship
Where possible, half the funding awarded by the foundation is allocated to Romanian students and researchers based in Romania or to help them relocate to France, and the remaining half is allocated to French or German researchers working in France (medicine) or Germany (music). Among the institutions whose profiles match these goals, IHU ICAN offers exceptional benefits, both in terms of its scientific work and commitment to hosting young Romanian researchers. Consequently, the founders of the Fondation Rhoe decided to support the IHU ICAN's work through a 10-year contract, establishing a University Chair of Cardiometabolism/NASH headed by Prof. Vlad Ratziu (Gastroenterology Consultant and Professor at Sorbonne University and Pitié Salpêtrière Hospital).

Marie-Astrid Raoult
Director of
the Carrefour Foundation
and the Group & France
Solidarity Division

As director of the Carrefour Foundation, I am proud to support the research project led by Dr Wilfried Le Goff at IHU ICAN, which explores links between obesity and diabetes. This study is fully in keeping with the Carrefour Foundation's mission. Since 2018, our foundation's charitable mission has been to promote the solidarity-based food transition based on three key areas: sustainable and solidarity-based farming, tackling food waste and societal commitment. Nutrition education is a fundamental component of our mission. Funding medical research means helping to formulate specific responses to food-related health issues, thus providing the necessary arguments to encourage individuals to eat a healthy and varied diet.
The Carrefour Foundation is keen to support both the treatment and prevention of obesity. IHU ICAN meets this challenge by elucidating the origins and causality mechanisms between obesity and diabetes.
Between 2018 and 2022, 650,000 people have improved their eating habits and switched to healthier diets thanks to the Carrefour Foundation's support for all its projects and particularly the IHU ICAN project.

FINANCIAL REPORT AND HR

HR

In 2022, IHU ICAN employed around 50 employees in research projects on cardiometabolic and nutritional diseases.

The HR division is involved in the 4 key areas of personnel administration, human relations, staff development and strategic HR management.

In 2022, it was able to embed the remote working policy and more effectively structure the process for new staff, from recruitment to full uptake of posts. Methodology, processes and tools are currently being reviewed as part of our ISO 9001 quality programme.

The training plan was implemented, including courses on emergency measures, fire safety, management, proficiency in English, and several legal aspects relating to AI and the GDPR.

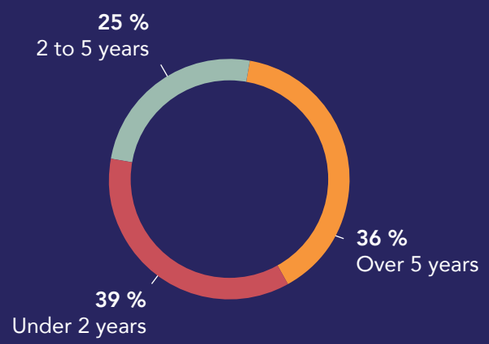
Key meetings were held to share information and communicate on the IHU's projects using various formats:

- 4 quarterly meetings to provide employees with a general briefing, including a 360° presentation of current and planned projects/ activities
- 3 themed meetings with a detailed presentation of a briefing or training session and an opportunity to discuss the topic
- 2 project reviews to present an overview of current scientific projects and focus on 2 research projects followed by an opportunity for scientific and strategic discussion

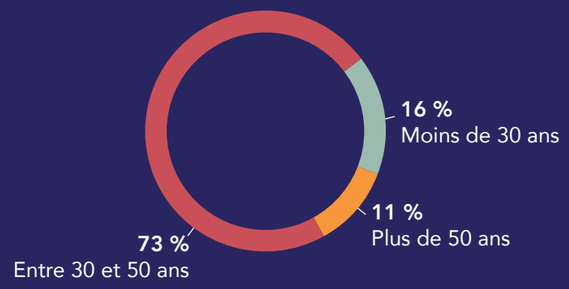
70% WOMEN

30% MEN

STAFF NUMBERS BY SENIORITY BRACKET



STAFF NUMBERS BY AGE BRACKET



BREAKDOWN BY DIVISION

(1) Imaging Platform and Clinical Investigation Platform

FINANCES

In 2022, the IHU continued its policy of prudent and careful financial management. The partnerships and fundraising policy was implemented to leverage new sources of funding for research activities. Through this approach, almost €600,000 was raised in 2022 to support the IHU ICAN research community's projects.

The development of industrial collaborations remains a priority and a key IHU strategic focus (54 studies in progress in 2022 with the launch of 18 clinical trials in the clinical investigation and MRI platforms and the completion of 5 trials). ICAN has maintained its capacity to respond to relevant European and domestic calls for proposals, enabling it to fund its community's scientific projects and thus pursue its roadmap by:

- **Cementing the key area of Cardiometabolic Imaging** by securing substantial IdF-BPI Sésame Filières funding (€1.5 million) for a heart-aorta multimodal imaging atlas project for the general population to investigate ageing within the CONSTANCES national epidemiological cohort.

- **Consolidating a key area involving the use of cohort data**
  > Structuring patient cohorts for:
  - non-alcoholic fatty liver disease (NAFLD)
  - hereditary heart disease (hereditary cardiomyopathies, dilated cardiomyopathies and arrhythmogenic right ventricular dysplasia)

  > Securing funding or initiating collaborations based on these cohorts:
  - European projects submitted in 2022 and awarded in 2023: DCM-NEXT for DCM and LIVERAIM for NAFLD,
  - industry funding (ISR) for a study modelling the simultaneous longitudinal evolution of non-invasive tests in addition to histological analysis of liver biopsies to investigate the progression or regression of NAFLD.
  - submission of a project aimed at developing multi-organ digital twins (industry/ academic/IHU France collaboration) for the Bpifrance i-Démo CFP

- **Submitting 2 projects** for the Data Challenge call for tenders from Health Data Hub, awarded in 2023, on predicting exacerbation of (1) HCM using genomic data (Cardi-HaCK) and (2) NAFLD using non-invasive testing.

◦ **Continuing projects in progress**

> European MAESTRIA project on atrial fibrillation (coordinated by Chief Executive, Professor Stéphane Hatem)

> Launch of several cardiology studies based, in particular, on cardiometabolic MRI imaging:

- Launch of the CATS-AF study and installation of an innovative ECG measuring device: the HRECG device developed by the Dutch company, YourRhythmics
- Launch of the CT-AF and ICARD studies

> Submission of the PEGASE project (first transatlantic heart transplant) to the ANSM and CPP

> Patent filed on preserving methylation when reprogramming somatic cells as induced pluripotent stem cells.

◦ **Developing international reach**

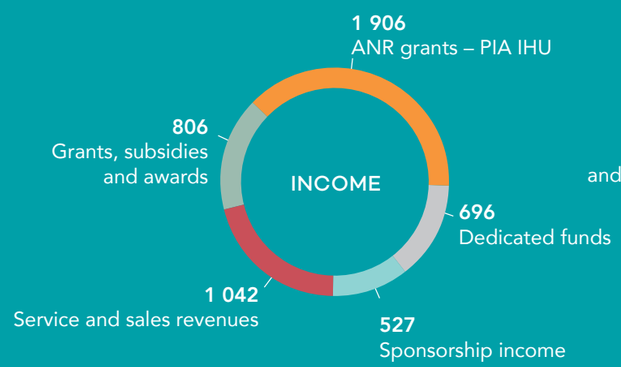
> Exporting the community's expertise and know-how by forging collaborations with public and private entities in the United Arab Emirates in relation to atrial fibrillation and NAFLD patient cohorts. This could be extended to incorporate a project to support the creation of a cardiometabolic institute in the United Arab Emirates.

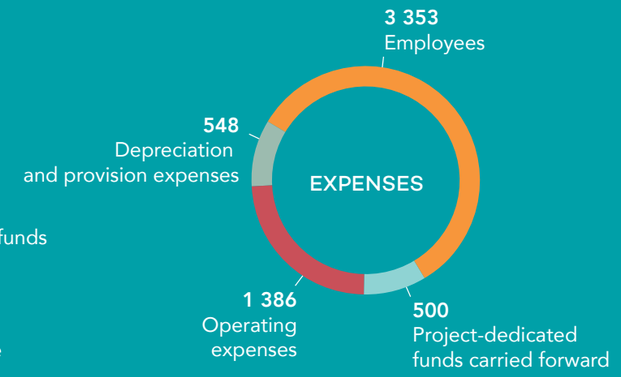
> Organising the first IHU ICAN summer camp for young researchers in partnership with the Cardiometabolic Health, Diabetes and Obesity Research Network (CMDO) in Quebec.

RESTATED INCOME STATEMENT	2022
Service revenues	1,042,463
Grants, subsidies and awards	805,619
ANR grant	1,906,613
Other revenues	1,223,028
of which sponsorship, financial contributions and donations (1)	526,768
of which use of project-dedicated funds	696,260
TOTAL OPERATING INCOME	**4,977,723**
Total operating expenses	(1,386,091)
Depreciation and provision expenses	(547,670)
Employees	(3,353,226)
Project-dedicated funds carried forward	(500,244)
TOTAL OPERATING EXPENSES	**(5,787,231)**
Financial profit/loss	12,437
Pre-tax profit/loss	(797,071)
Exceptional profit/loss	243,923
TOTAL INCOME	**5,455,962**
TOTAL EXPENSES	**(6,009,110)**
NET PROFIT/LOSS	**(553,148)**

(1) acquired through sponsorship activities

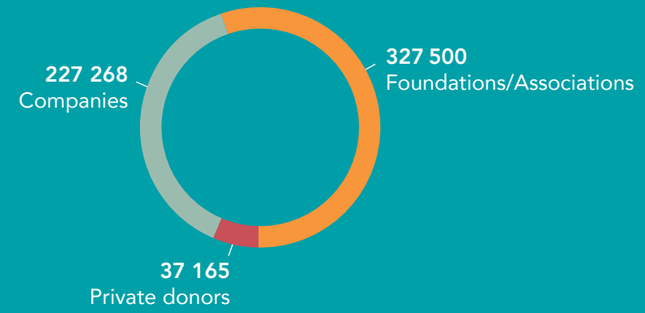
FOCUS ON INCOME AND EXPENSES





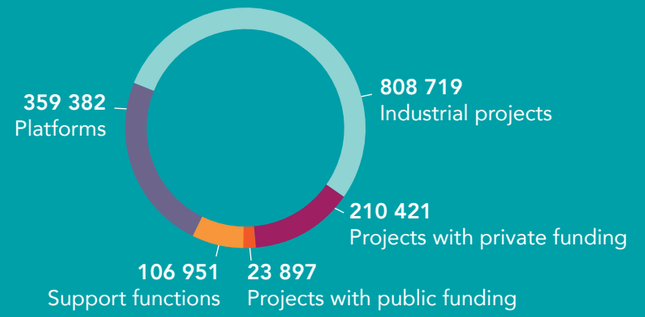
FOCUS ON SPONSORSHIP INCOME COLLECTED OVER THE YEAR

(neutralising the impact of the deferred income mechanism)[1]



FOCUS ON SERVICE REVENUES INVOICED IN 2022

(neutralising the impact of the deferred income mechanism)[1]



(1) The accounting mechanism for deferred income entails deferring some of the revenues earned over the year to a subsequent accounting year. This amount is therefore stated as a debit from the "income" accounts. In practical terms for ICAN, this relates to invoices that are issued during the year for the enrolment of patients in clinical trials and relate to trials that will only be completed in year N+1 or even subsequent years and sums paid into investigators' accounts for subsequent use of the portion of incoming donations allocated to an investigator's project.

PUBLICATIONS 2022

10 KEY ARTICLES FROM 2022

1. Charpentier E, Redheuil A, Bourron O, Boussouar S, Lucidarme O, Zarai M, Kachenoura N, Bouazizi K, Salem JE, Hekimian G , Kerneis M, Amoura Z, Allenbach Y, Hatem S, Jeannin AC , Andreelli F , Phan F; COVID-19 APHP. SU Group Cardiac adipose tissue volume assessed by computed tomography is a specific and independent predictor of early mortality and critical illness in COVID-19 in type 2-diabetic patients Cardiovasc Diabetol. 2022 Dec 31;21(1):294 PMID: 36587209

2. Levy D, Desnos C, Lebreton G, Théry G, Pineton de Chambrun M, Leprince P, Hammoudi N, Schmidt M, Combes A, Hékimian G Early Reversal of Right Ventricular Dysfunction after Venovenous Extracorporeal Membrane Oxygenation in Patients with COVID-19 Pneumonia Am J Respir Crit Care Med 2023 Mar 15;207(6):784-787 PMID: 36459095

3. Barhoum P , Pineton de Chambrun M, Dorgham K, Kerneis M, Burrel S, Quentric P, Parizot C, Chommeloux J, Bréchot N, Moyon Q, Lebreton G, Boussouar S, Schmidt M, Yssel H, Lefevre L, Miyara M, Charuel JL, Marot S, Marcelin AG, Luyt CE, Leprince P, Amoura Z, Montalescot G, Redheuil A, Combes A, Gorochov G, Hékimian G Phenotypic Heterogeneity of Fulminant COVID-19--Related Myocarditis in Adults J Am Coll Cardiol. 2022 Jul 26;80(4):299-312 PMID: 35863846

4. Soulat-Dufour L, Lang S, Addetia K, Ederhy S, Adavane-Scheuble S, Chauvet-Droit M, Jean ML, Nhan P, Ben Said R, Kamami I, Issaurat P, Capderou E, Arnaud C, Boccara F, Lang RM, Cohen A Restoring Sinus Rhythm Reverses Cardiac Remodeling and Reduces Valvular Regurgitation in Patients With Atrial Fibrillation J Am Coll Cardiol. 2022 Mar 15;79(10):951-961 PMID: 35272799

5. Pais R, Aron-Wisnewsky J, Bedossa P, Ponnaiah M, Oppert JM, Siksik JM, Genser L, Charlotte F, Thabut D, Clement K, Vlad Ratziu V Persistence of severe liver fibrosis despite substantial weight loss with bariatric surgery Hepatology. 2022 Aug;76(2):456-468 PMID: 35076966

6. Belda E, Voland L, Tremaroli V, Falony G, Adriouch S, Assmann KE, Prifti E, Aron-Wisnewsky J, Debédat J, Le Roy T, Nielsen T, Amouyal C, André S, Andreelli F, Blüher M, Chakaroun R, Chilloux J, Coelho LP, Dao MC, ..., Dumas ME, Stumvoll M, Pedersen OB, Bork P, Ehrlich SD, Zucker JD, Bäckhed F, Raes J, Clément K Impairment of gut microbial biotin metabolism and host biotin status in severe obesity: effect of biotin and prebiotic supplementation on improved metabolism Gut. 2022 Dec;71(12):2463-2480 PMID: 35017197

7. Pham A, Selenou C, Giabicani E, Fontaine V, Marteau S, Brioude F, David L, Mitanchez D, Sobrier ML, Netchine I Maintenance of methylation profile in imprinting control regions in human induced pluripotent stem cells Clin Epigenetics. 2022 Dec 28;14(1):190 PMID: 36578048

8. Montalescot G, Redheuil A, Vincent F, Desch S, De Benedictis M, Eltchaninoff H, Trenk D, Serfaty JM, Charpentier E, Bouazizi K, Prigent M, Guedeney P, Salloum T, Berti S, Cequier A, Lefèvre T, Leprince P, Silvain J, Van Belle E, Neumann FJ, Portal JJ, Vicaut E, Collet JP; ATLANTIS Investigators of the ACTION Group Apixaban and Valve Thrombosis After Transcatheter Aortic Valve Replacement The ATLANTIS-4D-CT Randomized Clinical Trial Substudy JACC Cardiovasc Interv. 2022 Sep 26;15(18):1794-1804 PMID: 36137682

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6. "Belda, E; Voland, L; Tremaroli, V; Falony, G; Adriouch, S; Assmann, KE; Raes, J; Clement, K & al» Impairment of gut microbial biotin metabolism and host biotin status in severe obesity: effect of biotin and prebiotic supplementation on improved metabolism Gut 2022 PMID 35017197

7. «Bouzid, D; Visseaux, B; Kassasseya, C; Daoud, A; Femy, F; Hermand, C; Simon, T; Freund, Y & al" Comparison of Patients Infected With Delta Versus Omicron COVID-19 Variants Presenting to Paris Emergency Departments A Retrospective Cohort Study Ann. Intern. Med. 2022 PMID 35286147

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