

ANNUAL REPORT 2021

IMAGINE, CURING GENETIC DISEASES



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EDITORIAL

A MESSAGE FROM THE DIRECTOR



2021 was a big year for *Imagine*! Despite having to contend with another year of pandemic-related constraints, the teams conducted their research with passion, talent and enthusiasm, maintaining publications at a very high level and deploying 'best-in-class' science to work towards the best future medicine for the benefit of families affected by genetic diseases.

Major discoveries have been made, contributing to a more effective understanding and treatment of many genetic diseases, as well as severe forms of Covid-19.

Highlights this year include a third success in bidding for an RHU (i.e., university-medical research) call for proposals for the Coviferon project, making us the only public-private player in France currently running three RHU projects. Elsewhere, achievements included a 50% success rate in ANR calls for proposals (double the national average), development of innovative clinical trials – including a world first in achondroplasia – three new start-ups selected by our Springboard project accelerator, and a record grant from Institut Carnot reflecting the dynamism of our industrial partnerships.

In these times of scientific and medical doubt and rumor, *Imagine* also reaffirmed its engagement with the wider world in June, at the first dedicated patient association forum, where we talked about what we know – or don't know – and how we do what we say.

This scientific and institutional momentum combined with a terrific surge in generosity. On December 8, 2021, we launched our first Major Donors Campaign. With €12 million of its ambitious €40 million target already raised, this will enable us to tackle the major challenges that lie ahead set out in our collective roadmap.

I would like to express my sincere gratitude to the wonderful tandem spearheading this vital campaign, Anne and Henri de Castries, and to all the friends they have managed to rally around the cause. However, their combat for *Imagine* goes even beyond this: they reaffirm our engagement with the wider world. Heartfelt thanks also to our other supporters and sponsors, our ambassador Teddy Riner, and our *Heroes* Committee – all ready to commit to another Gala evening in 2022. We are honored by the trust of these friends engaged alongside us.

Together, along with our founders, we constitute the foundation on which the sustainability of our University-Medical Institute (*IHU*) business model is built.

French *IHUs* were created in 2011 to integrate biomedical research of excellence with a translational focus. Their mission is to develop the care and research pathways and corresponding industrial sectors of the future. Ten years later, this model – which treats biomedical research not as an additional cost but as an investment in the future – has demonstrated all of its value. Its development formed part of the French government's Health Innovation 2030 plan, which aims to make France the leading European nation in this field. We are proud to be part of this national strategy as one of the six *IHUs* currently comprising the *IHU-France* alliance.

However, scientific and medical excellence – the *sine qua non* of our long-term sustainability, would exist in isolation if they were not allied with *Imagine's* other founding values, namely humility and sincerity, generosity and engagement with the wider world.

Prof. Stanislas Lyonnet,
Director, Institut *Imagine*

EDITORIAL

A MESSAGE FROM THE PRESIDENT



Duties and responsibilities of French IHUs

Certain trials make us stronger. Institut Imagine has emerged from the pandemic with an even greater sense of institutional community. Just as some people are more resistant than others to the virus, some institutes are better equipped to deal with major challenges thanks to a common DNA and a strong sense of a 'community of destiny', as Ernest Renan described in 'What is a nation?'

The secret of the DNA of French IHUs is contained not in four letters but in four watchwords: proximity, reactivity, flexibility and loyalty. The first three are attributable to our status as a private Scientific Research Foundation that brings together both public and private partners. This is by no means unique and it is the approach that has made the large campuses in prestigious Anglo-Saxon universities so successful. The last of our 'good genes' is loyalty to the founding institutions who have put all their trust in us, namely Université Paris Cité, Inserm and AP-HP (the Paris public hospitals authority). Loyalty and immense gratitude to the Campaign Committee, its

presiding couple and all the major donors who have taken up the cause of *Imagine's* children.

Loyalty and gratitude too to all the vital founders of our institution, namely the Hospitals Foundation, AFM-Telethon and the City of Paris.

Trust is earned and needs to be maintained if it is to be renewed.

Our oversight bodies expect us to demonstrate the feasibility of our business model over the term of the Investment in the Future programs. They expect us to continually enhance our scientific profile, as borne out by our increased attractiveness to major international scientific leaders, both at Institute management level and at the head of the research teams whose contracts are being renewed. They expect *Imagine* to fulfill its role of providing honest information about the scientific progress we are making and its expected benefits. And, last but not least, they expect genuine sharing of progress.

Progress cannot be the privilege of a select few and true progress really means progress shared.

Prof. Arnold Munnich,
President, Fondation *Imagine*

A MESSAGE FROM THE FOUNDERS



Institut Imagine is seven years old! Seven years, the age of reason, and time to look to the future, which I see as presenting limitless possibilities. We have already reached extraordinary and remarkable heights because

Imagine brings together the three essential and inter-dependent dimensions in understanding genetic diseases and relieving or – better still – curing them: a clinical component, research and humanism.

I would like to congratulate all Imagine's stakeholders and they join with me in thanking all those who have helped us and will go on helping us into the future.

Prof. Claude Griscelli
Founding President



I see Institut Imagine as a tree that has succeeded in combining its different roots in research and medicine for the benefit of patients.

I have been fortunate enough to watch this tree and this rare spirit grow, nurtured by shared values and a common vision, technological, financial and human resources, and an international and multicultural environment.

I believe that Imagine's future lies in its ability to renew itself, to reach out and to continue to be attractive to young people.

Prof. Alain Fischer
Founding Director

EDITORIAL

A MESSAGE FROM THE EXECUTIVE MANAGER



Genetic diseases are a major public health issue, not only because of the number of people they affect, but also due to their impact on day-to-day living, over and above treatment issues. They challenge the place of patients in society and in the family, social and professional spheres. As a unique body combining expertise, commitment and innovation in the service of patients suffering from rare genetic diseases, Institut Imagine needs to broaden its focuses and actions by engaging even more with patients, their associations, the general public and its academic and socio-economic partners.

Together, we have a mission that is especially dear to our hearts: developing a more human vision of genetics and genomics to improve the quality of life of patients and their families in all areas, and to do everything possible to enable them to live better lives with their disease.

For the past three years, our program dedicated to the societal role of Institut *Imagine* has been working on ways to be more engaged with society and the human and social sciences. A number of programs have been launched: in health economics with the Hospinnomics Chair (*AP-HP, PSE*) dedicated to the costs of misdiagnosis; in health design with EnsAD around invisible disabilities, the symbolization of the Institute and health visualization methods; and in outreach programs for young people suffering from genetic diseases with 'La Suite' program at the Necker Public Hospital for sick children in Paris.

Laure Boquet,
Executive Manager, Institut *Imagine*

Two calls for proposals in the human and social sciences – rare diseases – were launched for multi-disciplinary and multi-professional collaborative research projects aimed at improving the quality of life of patients and three projects were rolled out in 2021. This year, we are proud to have been able to get the very first dedicated patient association forum – *FAIR* – up and running. It marks the beginning of greater engagement and outreach to patient organizations in Institut *Imagine* projects and strategy.

The Institut's engagement is aimed especially at young people. Its programs to train the doctors and researchers of tomorrow were revamped in 2021, in particular through our 'PPU@*Imagine*' (Pasteur Paris University) partnership with Institut Pasteur to host international doctoral students. Awareness on the part of the general public and young people has been boosted by a new program of grants to disseminate scientific knowledge, supported by our doctoral students eager to pass on their knowledge and enabling us to reopen our doors to the public and create a program for hosting ninth-grade high school interns.

These projects aim to provide support for families, to help them live with the illness when science and medicine cannot provide any immediate answers. Institut *Imagine* is a unique place and its model encourages fertile exchanges and meetings between different forms of expertise and academic disciplines – all for the benefit of patients.

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INSTITUT *IMAGINE* TIMELINE

2007

Fondation *Imagine* created by AP-HP (Paris public hospitals authority), Inserm, Université Paris Cité, Fondation des Hôpitaux, the City of Paris and AFM-Téléthon. The founding President was Prof. Claude Griscelli and the first Director Prof. Alain Fischer.

2009

Establishment of International Scientific Advisory Board, chaired by Elizabeth Blackburn, Nobel Prize in Medicine, 2009.

2014

Inauguration of the *Imagine* building
Merger of founding research team into a single mixed research unit (UMR 1163).

2012

Teddy Riner becomes an ambassador for Institut *Imagine*.
First international recruitment program.

2011

Imagine gets Institut Hospitalo-Universitaire status (IHU – University Medical Institute) as part of the French Government Investments for the Future (PIA) Program.

2015

First *Heroes for Imagine* gala, followed by similar events in 2016 and 2018.
Graduation of first intake of international PhD students.

2016

Prof. Stanislas Lyonnet becomes Director of Institut *Imagine*, and Prof. Arnold Munnich becomes President of Fondation *Imagine*.
Tremplin Carnot label awarded.

2017

Launch of C'IL-LICO 'Medicine of the future for ciliopathies with renal impairment' university-medical research project.

2019

Launch of RHU ATRACtion 'Primary immunodeficiency with autoimmunity or autoinflammation' university-medical research project.
Evaluation of the University-Medical Institutes by an international jury and the General Secretariat for Investment (SGPI) and extension of the IHU label through 2024 by decision of the French Prime Minister.

2018

Successful evaluation of the Institut's research labs by the High Council for Evaluation of Research and Higher Education (HCERES).

2020

Institut Carnot label awarded.

2021

Imagine successfully tenders for a third RHU project – 'Coviferon'.
Launch of the Institut's first Major Donors Campaign.

KEY FIGURES
2021

1,000

RESEARCHERS AND CARE PROFESSIONALS UNITED AROUND THE SAME OBJECTIVE

31%

COMPRISE PHD, POST-DOCTORAL CANDIDATES AND UNDER GRADUATES

37

NATIONALITIES

6

INTEGRATED CARE AND RESEARCH PROGRAMS (ICARPS)

2

CLINICAL INVESTIGATION CENTERS

31

AFFILIATED REFERENCE CENTERS FOR RARE DISEASES

OVER

500

CLINICAL TRIALS IN PROGRESS IN UNIVERSITY MEDICAL RESEARCH

8

AFFILIATED HOSPITAL UNITS

OVER

30,000

IN SITU CONSULTATIONS

1,031

SCIENTIFIC PUBLICATIONS IN THE AREA OF UNIVERSITY-MEDICAL RESEARCH

18

TECH PLATFORMS

24

IN SITU RESEARCH TEAMS

4

ASSOCIATED LABS AT THE NECKER PUBLIC HOSPITAL FOR SICK CHILDREN

52

FAMILIES OF PATENTS AND ACTIVE SOFTWARE

OVER

€5.6 MILLION

COLLECTED (IN DONATIONS, PRIVATE GRANTS AND PHILANTHROPY)

€1.2 MILLION

WORTH OF INDUSTRIAL CONTRACTS

IMAGINE'S SIX FOUNDING MEMBERS:



OUR GOVERNANCE

Institut *Imagine* is supported by a Scientific Research Foundation (FCS) set up in 2007 by the six founding members. This private structure is able to manage both public and private funds and its status provides flexibility and responsiveness by combining the best of the public and private sectors.

Imagine secured University-Medical Institute (IHU) accreditation in 2011, allowing it to receive an endowment under the French Government Investments for the Future (PIA) Program. This accreditation has been extended through 2024. A new evaluation will take place in 2023 with a view to extending these investments.

Imagine has also had Institut Carnot accreditation from the French Ministry of Higher Education, Innovation and Research since 2020.



Our founding members

Imagine has benefited from the support of its six founding members since its creation and we would like to thank them for their support and trust year in, year out.



Our governance bodies

Fondation *Imagine* has a Governing Board comprising the six founding member institutions, qualified experts selected by them, as well as representatives elected by the Foundation's academic staff, researchers, lecturer-researchers and employees. Two new members joined the Board in 2021: Aline Sylla-Walbaum, CEO of Christie's France, and Philippe Wahl, CEO of La Poste Group.

The Director of the Institute is supported by a joint Executive Committee made up of researcher and clinician representatives from *Imagine's* different research and care programs. The Executive Committee was renewed in 2021 following the departure of three members and four new incoming members.

The IHU Board brings together the heads of research labs and staff representatives to discuss the main scientific focuses and how the Institute is run on a day-to-day basis.

In September 2021, Institut Imagine advertised for applications for its next Director-elect to be appointed on January 1, 2023 for a five-year term as Director of the Institute, beginning on January 1, 2025.

Economic and Social Committee (CSE)

The CSE gives a collective voice to employees to ensure that their interests are reflected in decisions concerning the management and economic and financial development of the Institut, as well as the organization of work, professional training and production techniques. The CSE was set up in June 2019.

INTERNATIONAL SCIENTIFIC ADVISORY BOARD

The International Scientific Advisory Board comprises eminent, internationally-renowned scientists and it issues annual recommendations to the Governing Board and *Imagine* Management regarding the Institut's scientific and strategic focuses, covering the selection of new teams, the development and organization of scientific groups and the assessment of their work. In 2021, it met virtually on two occasions, in May and December.



A message from Elizabeth Blackburn, Chair of the International Scientific Advisory Board in December 2021

'The International Scientific Advisory Board is proud to note that the Imagine model – combining clinical and biological components – continues to demonstrate its effectiveness. For us, the Institute is a treasure, perhaps unique anywhere, with its strategy of subjecting rare diseases to biological investigation, combined with a strong translational research program. It has made great strides in all of these areas since it was set up.'

Composition of the Scientific Advisory Board



Prof. Elizabeth Blackburn
Awarded the 2009 Nobel Prize in Medicine
Department of Biochemistry and Biophysics, University of California, San Francisco, USA



Prof. Stylianos Antonarakis
Department of Medical Genetics, University of Geneva, Geneva Faculty of Medicine, Switzerland



Prof. Aravinda Chakravarti
NYU Grossman School of Medicine, New York, USA



Prof. Iain Drummond
MDI Biological Laboratory Bar Harbor, USA



Prof. Denis Duboule
Laboratory of Developmental Genomics, Lausanne, Switzerland



Prof. Douglas Higgs
The MRC Weatherall Institute of Molecular Medicine, Oxford University, UK



Prof. Bernard Malissen
Director of the Center for ImmunoPHEnomics (CIPHE) Marseille-Luminy, France



Dr. Anthony Monaco
Tufts University, Medford/Somerville, USA



Prof. Fiona Powrie
Kennedy Institute of Rheumatology, Oxford University, UK



Prof. Antoine Triller
Biology Institute of Ecole Normale Supérieure, Paris, France

A TEN-YEAR SCIENTIFIC AND STRATEGIC ROADMAP

Nearly 8,000 different genetic diseases have been recorded to date and new ones are constantly being discovered. In Europe alone, over 35 million people are affected – the figure in France is one person in twenty. While 30,000 new people are affected every year in France, more than 50% have no diagnosis and there is no specific curative treatment in 85% of cases.

To tackle this public health issue, *Imagine* has set out ambitious goals in its 'Imagine 2018- 2028' ten-year roadmap. These objectives were adjusted in 2020 following the announcement in late 2019 of the extension of University-Medical Institute (*IHU*) accreditation and funding for 2020-2024 as part of the French Government Investments for the Future (*PIA*) Program. They will undoubtedly be adjusted once more in 2023 when a request for extension of *IHU* funding will be submitted as part of the 'Plan Santé Innovation 2030' government investment program.

A single goal: changing the lives of families affected by genetic diseases

Imagine's great strength is the fact that it brings together in the one place 28 research teams – or 24 integrated research labs and 4 associated labs – 18 tech platforms, 31 affiliated reference centers for rare diseases and 8 clinical research units from Necker, Cochin and HEGP public hospitals. By bringing together all of these different stakeholders, *Imagine* creates an environment conducive to going further and faster by organizing activities as part of a single 'loop' comprising clinical observation of patients and understanding the causes and mechanisms of diseases, thus accelerating new diagnoses and treatments.

Ten-year objectives

- ▶ Reducing delays in patient diagnosis by increasing rates of diagnosis to 80%,
- ▶ Doubling the number of research avenues and projects that focus on how diseases actually work,
- ▶ Doubling the number of clinical trials to ultimately provide access to such trials for 30% of patients, and doubling the available therapeutic solutions,
- ▶ Discovering common means of treating groups of diseases,
- ▶ Continuing to enrich the Institute's remarkable cohorts, which are the starting point for all research and future progress,
- ▶ Continuing to deploy an outward-looking approach and scientific resourcing, especially internationally, by recruiting new teams and developing collaborative projects and initiatives that are open to the human and social sciences,
- ▶ Investing in technological innovation,
- ▶ Accelerating bioinformatics, genomics, and data processing programs,
- ▶ Supporting students and young researchers with a structured academic offer, career support, and mentoring,
- ▶ Creating a center for modeling genetic diseases using AI and digital twins, combining clinical, genome and research data as well as lived experience,

A number of the initiatives outlined in this project were deployed in 2021 in pursuit of these goals.



Six integrated care and research programs

The bulk of Institut *Imagine's* resources will be focused on six priority areas over the next few years (see the following page). Each of these major initiatives harnesses all of the requisite talent, research teams, tech platforms, associated research labs, reference centers for rare diseases and clinical research units, working to international standards of excellence.

Immunology-infectology: diseases of the immune system and genetic predispositions to infections, affecting one in 5,000 children in France.

Neurological and neurodevelopmental diseases: nearly 2% of children are affected.

Hematology: diseases in blood cells, including the world's most common genetic disease – sickle cell anemia.

Development abnormalities and cardiology: 2% to 3% of births are affected by a congenital malformation or developmental illness.

Nephrology: more than 150 kidney diseases are attributable to genetic alteration.

Data science: unleashing clinical and biological data and exploring still unknown areas using bioinformatics and artificial intelligence to deploy the medicine of the future.

SIX PRIORITY CARE AND RESEARCH PROGRAMS

1 NEPHROLOGY

RESEARCH LABORATORIES

- Hereditary kidney diseases ▶ **S. Saunier**

REFERENCE CENTERS FOR RARE DISEASES

- Hereditary kidney disease in children and adults ▶ **L. Heidet**
- Thrombotic microangiopathies ▶ **A. Servais**
- Idiopathic nephrotic syndrome ▶ **B. Knebelmann and O. Boyer**

AFFILIATED CLINICAL DEPARTMENTS AT THE NECKER PUBLIC HOSPITAL FOR SICK CHILDREN

- Nephro-transplantation ▶ **D. Anglicheau**
- Pediatric nephrology ▶ **R. Salomon**

2 NEUROLOGICAL AND NEURODEVELOPMENTAL DISEASES

RESEARCH LABORATORIES

- Developmental brain disorders ▶ **V. Cantagrel**
- Translational research into neurological disorders ▶ **E. Kabashi**
- Genetics and development of the cerebral cortex ▶ **A. Pierani**
- Genetics of mitochondrial diseases ▶ **A. Rötig**
- Genetics in ophthalmology ▶ **JM. Rozet**

ASSOCIATED RESEARCH LABS

- Image@*Imagine* multi-modal brain imaging ▶ **N. Boddaert**

REFERENCE CENTERS FOR RARE DISEASES

- Rare forms of intellectual impairment ▶ **M. Rio**
- Rare forms of intellectual impairment – multiple disabilities ▶ **N. Bahi-Buisson**
- Rare eye diseases ▶ **D. Brémond-Gignac**
- Hereditary metabolic diseases ▶ **P. de Lonlay**
- Mitochondrial diseases from adults to children ▶ **JP. Bonnefont**
- Rare epilepsies ▶ **R. Nabbout**
- Neuromuscular diseases North/East France/Paris Region ▶ **I. Desguerre**

3 IMMUNOLOGY-INFECTOLOGY

RESEARCH LABORATORIES

- Human genetics of infectious diseases: complex predisposition ▶ **L. Abel**
- Human genetics of infectious diseases: monogenic predisposition ▶ **JL. Casanova**
- Intestinal immunity ▶ **N. Cerf-Bensussan**
- Neurogenetics and neuroinflammation ▶ **Y. Crow**
- Lymphocyte activation and sensitivity to Epstein-Barr virus ▶ **S. Latour**
- Inflammatory responses and transcriptomic networks in diseases ▶ **M. Ménager**
- Molecular basis of altered immune homeostasis ▶ **G. Ménasché and F. Sepulveda**
- Immunogenetics of pediatric autoimmune diseases ▶ **F. Rieux-Laucat**
- Dynamics of the genome in the immune system ▶ **JP. de Villartay and P. Revy**

REFERENCE CENTERS FOR RARE DISEASES

- Hereditary immunodeficiencies ▶ **N. Mahlaoui et A. Fischer**
- Rare digestive tract diseases ▶ **F. Ruemmele**
- Inflammatory rheumatism and rare systemic autoimmune diseases in children ▶ **P. Quartier dit Maire**

AFFILIATED CLINICAL DEPARTMENTS AT THE NECKER PUBLIC HOSPITAL FOR SICK CHILDREN

- Pediatric immunohematology and rheumatology ▶ **P. Quartier dit Maire**
- Infectious and tropical diseases ▶ **O. Lortholary**

4 HEMATOLOGY

RESEARCH LABORATORIES

- Human lymphohaematopoiesis ▶ **I. André**
- Cellular and molecular mechanisms involved in hematological disorders and therapeutic implications ▶ **O. Hermine**
- Chromatin and gene regulation during development ▶ **A. Miccio**

REFERENCE CENTERS FOR RARE DISEASES

- Pediatric hemophilia ▶ **A. Harroche**
- Mastocytosis ▶ **O. Hermine**
- Major sickle cell syndromes ▶ **M. de Montalembert**

AFFILIATED CLINICAL DEPARTMENTS AT THE NECKER PUBLIC HOSPITAL FOR SICK CHILDREN

- Innovative therapies ▶ **M. Cavazzana**
- Adult hematology ▶ **O. Hermine**

5 DATA SCIENCE AND COMPUTER-ASSISTED DECISION MAKING

RESEARCH LABORATORIES

- Clinical bioinformatics ▶ **A. Rausell**

AFFILIATED DEPARTMENTS AT THE NECKER PUBLIC HOSPITAL FOR SICK CHILDREN

- Federation of medical genetics
- Medical Informatics ▶ **A. Burgun**

6 DEVELOPMENT & CARDIOLOGY

RESEARCH LABORATORIES

- Embryology and genetics of malformations ▶ **J. Amiel & S. Lyonnet**
- Genetic skin diseases: from disease mechanisms to therapy ▶ **A. Hovnanian**
- Molecular and pathophysiological bases of osteochondrodysplasia ▶ **L. Legeai-Mallet and V. Cormier-Daire**
- Heart morphogenesis ▶ **S. Meilhac**

ASSOCIATED RESEARCH LABS

- Molecular bases of severe congenital and neonatal endocrine disorders and new therapeutic strategies ▶ **M. Polak**
- Imag2 computational anatomy for image-guided minimally invasive surgery in pediatric tumoral and developmental diseases ▶ **S. Sarnacki and I. Bloch (Télécom ParisTech)**

REFERENCE CENTERS FOR RARE DISEASES

- Pierre Robin syndrome and congenital sucking and swallowing disorders ▶ **V. Abadie**
- Developmental abnormalities and malformation syndromes ▶ **J. Amiel**
- Rare skin and mucous membrane diseases of genetic origin ▶ **C. Bodemer**
- Complex congenital heart defects ▶ **D. Bonnet**
- Constitutional bone diseases ▶ **V. Cormier-Daire**
- Rare ENT malformations ▶ **F. Denoyelle**
- Genetic deafness ▶ **S. Marlin**
- Clefts and facial malformations ▶ **A. Picard**
- Rare gynecological pathologies ▶ **M. Polak**
- Rare anorectal and pelvic disorders ▶ **S. Sarnacki**
- Craniosynostoses and craniofacial malformations ▶ **G. Paternoster**
- Rare vertebral and spinal malformations ▶ **S. James**
- Cardiomyopathies and hereditary cardiac rhythm disorders ▶ **A. Hagège**
- Cardiomyopathies in neuromuscular diseases North/East France/Paris Region ▶ **K. Whabi**
- Rare anorectal and pelvic diseases (MAREP) ▶ **C. Cretolle**

CLINICAL AND TECHNOLOGICAL BASE

CLINICAL RESOURCES AT THE NECKER PUBLIC HOSPITAL FOR SICK CHILDREN

- 1 clinical investigation center for biotherapies ▶ **M. Cavazzana**
- 1 'mother and child' multi-thematic clinical investigation center ▶ **JM. Tréluyer**

RESEARCH SUPPORT PLATFORM (*IMAGINE*)

- 1 investigation team
- 1 promotional team

18 TECH PLATFORMS OPERATED WITH THE SUPPORT OF SFR NECKER US-24, INEM (INSTITUT NECKER-ENFANTS MALADES) AND *IMAGINE*'S FOUNDING MEMBERS

- Imagine*: Data Sciences, IPS (induced pluripotent stem cells), rAAV, IRM3T, Single-Cell@*Imagine*, electrophysiology
- SFR Necker/*Imagine*: genomics, bioinformatics, biological resource center, proteomics, cytometry, cell imaging, histology, viral vectors and gene transfer, animal treatment, small animal transgenics, electrophysiology, metabolomics, neurobehavior.



HIGHLIGHTS

Acceleration and innovation

- **Extension of Institut *Imagine*'s scientific and clinical brief:** recruitment of an international research team, six new reference centers for rare diseases*, a new affiliated clinical department* to support the goals of the Fast4Kids program, i.e., harnessing genomic, clinical and cellular data to accelerate research into genetic diseases. (*located at Necker, Cochin and HEGP public hospitals. Centre Université Paris Cité).
- 50% **success rate in bidding for ANR calls for proposals** (compared to a national average of 23%).
- More than **500 clinical trials** in progress.
- **3 start-up projects** selected by the Springboard project accelerator.
- 3 projects selected by the Carnot Committee for **Innogrants** (innovation grants) plus a doubling of Carnot funding.
- **1031 scientific publications.**
- A **world first in the treatment** of achondroplasia.
- **Major advances in research into genetic diseases**, including the identification of a therapeutic molecule for Friedreich's ataxia, identification of mutations in the ANKRD17 gene in patients with intellectual impairment, development of a bioinformatics-based method for generating cellular ID cards, and development of new gene therapy vectors to combat sickle cell disease.

Continuing the fight against Covid-19

- Successful bid for an *RHU* (i.e., university-medical research) call for proposals for the **Coviféron project**, headed up by Prof. Jean-Laurent Casanova and Dr. Laurent Abel.
- Major discoveries concerning the **genetic and autoimmune origins of severe forms of Covid-19**, accounting for more than 20% of severe forms and mortalities.
- Major discoveries concerning an **immunological signature of severe Covid-19** and a molecular profile of pediatric myocarditis linked to Sars-Cov-2.



International

- Recruitment of a **new team to carry out research** into the genetics of neurodevelopment following an international call for tenders.
- Revamping of the **training program for international PhD students**, PPU@Imagine: over 200 applications, 3 successful candidates recruited in 2021, 4 for the beginning of the 2022 academic year.



Reaching out

- Launch of a program to **disseminate scientific knowledge**, spearheaded by our doctoral students.
- **First dedicated patient association forum – FAIR** – Forum of Associations of patients who '*Imagine*' what Research means.
- 3 years of the **program to reach out to the Human and Social Sciences and promote the societal role** of Institut *Imagine*, launch of a second call for projects.
- Launch of a **socio-professional outreach program** for young people suffering from genetic diseases.
- **The Institute reopened its doors to the public:** day-long seminar on rare diseases, Heritage Day, science festival, etc.

Development

- Launch of the **Major Donors Campaign**, headed up by Anne and Henri de Castries. Aim: to raise €40 million over 5 years. €12 million have already been collected.
- Many **new research projects** launched or supported with the help of our donors.
- Mobilization of our **ambassador Teddy Riner** who paid a visit to the Institute to support our researchers, foster awareness and give a boost to the end-of-year fundraising drive.

PRIZES AND DISTINCTIONS



- **Prof. Jean-Laurent Casanova, Director of the Human genetics of infectious diseases research lab**
Awarded the Abarca Prize
- **Prof. Marina Cavazzana, Director of the CIC-BT clinical investigation center and head of the affiliated bioterapy department (Necker Hospital)**
Fred Saunders Lectureship Award from the Canadian Society for Cellular and Gene Therapy
- **Prof. Alain Hovnanian, Director of the genetic skin diseases research lab**
EURORDIS Black Pearl 2021 scientific award
- **Thuy-Linh Le, PhD student at the Embryology and genetics of malformations research lab**
Prix de la Chancellerie des universités de Paris – Thesis prize
- **Prof. Stanislas Lyonnet, Director, Institut *Imagine***
Appointed *Officier de la Légion d'Honneur* in 2021
- **Dr Annarita Miccio, Director of the Chromatin and gene regulation during development research lab**
Outstanding new researcher of 2021, awarded by the American Society for Cell and Gene Therapy (ASCGT)
- **Isabelle Perrault, Researcher at the Ophthalmological genetics research lab**
Prix de l'œil (awarded by *Fondation de l'œil*)
- **Prof. Sabine Sarnacki, Director of IMAG2 research lab, affiliated to Institut *Imagine***
Appointed *Officier de la Légion d'Honneur* in 2021



DISCOVERY

'All of our efforts and energy go into ensuring that, if a discovery is made, it doesn't get bogged down by processes and can be immediately put to work for care and clinical research. This is Imagine's raison d'être: accelerating the timeline between patient needs and therapeutic response, through research of excellence.'

Prof. Stanislas Lyonnet,
Director, Institut *Imagine*

From patient to lab table – and from lab table to patient – doctors, researchers and engineers at Institut *Imagine* are relentlessly trying to decipher the ways in which genetic diseases work in order to enhance diagnosis and identify new therapeutic targets. 2021 was an especially busy year in our labs and here is a summary of the key developments.

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01

JANUARY

EPILEPSY: USING ARTIFICIAL INTELLIGENCE TO IDENTIFY SIMILAR-TYPE PATIENTS

Thanks to 'Dr Warehouse' – a smart biomedical data warehouse developed by Nicolas Garcelon, Director of the Data Science platform which has collated the clinical reports of some 820,000 patients, the 'Translational research for neurological disorders' team headed up by Edor Kabashi and Prof. Rima Nabouh, was able to identify two patients sharing very specific characteristics with the same de novo mutation of the *KCNA2* gene present in a rare form of epilepsy. This technology should eventually help to identify patients with similar genetic diseases and thus build consistent cohorts. No mean feat for clinical research into rare diseases!

M. Hully et al., *Genet Med*, 2021, pubmed.ncbi.nlm.nih.gov/33500571/

111
02

FEBRUARY:

CILIOPATHIES WITH RENAL IMPAIRMENT

Dr. Laurence Heidet of the 'Hereditary kidney disease' lab headed up by Dr. Sophie Saunier, has demonstrated that recessive mutations in both copies of gene *DNAJB11* cause Ivemark II syndrome, leading to enlarged kidneys, dilatation and proliferation of pancreatic duct cells and liver malformation. By observing kidney tissue taken from patients with these mutations, the team was able to demonstrate that the lesions observed were typical of ciliopathies, a group of diseases affecting the primary cilium, an antenna-like structure on the surface of most of our cells. The cilia of renal tubular cells in particular were

abnormally long and deformed. This is a major discovery for developing future therapeutic strategies.

P. Jordan et al., *Kidney Int.*, pubmed.ncbi.nlm.nih.gov/33129895/

FROM CELIAC DISEASE TO LYMPHOMA

Celiac disease is a common auto-immune intestinal disease triggered by eating gluten. Most patients recover by adopting a strict gluten-free diet, however, a rare and severe complication can arise: the development of lymphoma. Following an in-depth analysis of the genetic profile of the malignant cells, the 'Intestinal Immunity' team led by Dr. Nadine Cerf-Bensussan, identified Gain-of-Function Mutations in *JAK1* and *STAT3* genes, which are involved in the survival and proliferation process triggered by inflammatory factors present in the intestine. These give a selective advantage to malignant lymphoma cells that gradually replace and eliminate immune cells in the intestine. These findings reveal potential therapeutic targets and partly explain how chronic inflammation associated with autoimmunity can lead to lymphoma formation.

S. Cording et al., *Gut*, pubmed.ncbi.nlm.nih.gov/33579790

53 % !

This is the rate of diagnosis obtained in a group of patients with congenital hypothyroidism and dysmorphogenesis (an abnormal thyroid) thanks to the 'HypoHseq' gene panel set up at Institut *Imagine* by the team of Prof. Michel Polak, Director of the 'Molecular bases of severe congenital and neonatal endocrine disorders' research lab. Using targeted next-generation sequencing, the researchers identified mutations that are highly likely to be pathogenic, especially in *TG*, *DUOX2*, *DUOX1* and *NIS* genes.

A. Stoupa et al., *Front Endocrinol*, 2021, pubmed.ncbi.nlm.nih.gov/33692749/



INSIDE A BABY'S BRAIN

The very first year of life is a crucial period for brain development, characterized by fairly spectacular structural and functional modifications. To understand the dynamics at work more effectively, the team led by Prof. Nathalie Boddaert, Director of the Image@*Imagine* laboratory, affiliated to Institut *Imagine*, used ASL-MRI to measure changes in blood flow through the brains of 52 small infants when at rest, throughout the first year of life. The findings highlight key stages in local functional brain maturation and are consistent with what we know about infant cognitive development. This work on non-pathological brain development is essential for a clearer understanding of pathological developments observed in several neurodevelopmental diseases, including Duchenne disease, autistic disorders, and Prader-Willy syndrome.

H. Lemaître et al., *Cereb Cortex*, 2021, pubmed.ncbi.nlm.nih.gov/33230520/

A NATURAL HISTORY OF ACROMICRIC DYSPLASIA

Geophysical dysplasia (GD) and acromicric dysplasia (AD) are characterized by short stature, short limbs and progressively stiff joints. In GD, cardiorespiratory incidents can lead to premature death. Dominant heterozygous mutations in genes *FBN1* and *LTBP3* are responsible for both diseases, whereas recessive variants in gene *ADAMTSL2* are responsible only for GD. In a retrospective study on 22 patients suffering from these two rare diseases, Prof. Valérie Cormier-Daire's team was able to determine the natural history and

establish genotype-phenotype correlations that paved the way for specific multi-disciplinary monitoring.

P. Marzin et al., *Genet Med*, 2021, pubmed.ncbi.nlm.nih.gov/33082559/

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03

MARCH:

A KEY ROLE FOR GENE *WDR73*

Several studies have found that mutations in gene *WDR73* are at the root of Galloway-Mowat syndrome, a rare disorder characterized by neurological defects and a kidney disease that affects the glomerulus, the kidney's filtering system. Dr. Géraldine Mollet from Prof. Corinne Antignac's 'Hereditary kidney diseases' research team has highlighted interactions between the protein encoded by this gene and two subunits of a protein complex known as Integrator, which plays a key role in the metabolic process of small RNAs and in regulating the transcription process. The team also demonstrated that deleting *WDR73* modifies the expression of gene coding for cell cycle regulatory proteins. This interferes with cellular pathways that are essential for the survival of cells after cell division, especially cells of the kidney glomerulus known as 'podocytes' or neurons. These pathways are therefore interesting therapeutic targets for the prevention of degenerative diseases.

F.C. Tilley et al., *Sci Rep*, 2021, pubmed.ncbi.nlm.nih.gov/33686175/

A NEW LINK BETWEEN TWO DISEASES

The 'Molecular basis of altered immune homeostasis disorders' research lab headed up by Dr. Gaël Ménasché and Dr. Fernando Sepulveda, in liaison with the Department of Neurology of Montpellier, has established a link between a neurological disease known as CLIPPERS, and an immunogenetic disease that causes hyperinflammation of the immune system – hemophagocytic lymphohistiocytosis (HPL). The researchers spotted that one-third of patients with CLIPPERS-type syndrome have mutations in one of the HLH genes involved in the cytotoxic activity of lymphocytes, an essential function of the immune system in fighting off infection. As more targeted immunosuppressive therapies have recently been developed for HLH, it could be beneficial to evaluate their effectiveness in combating CLIPPERS syndrome.

G. Taieb et al., *Neurol Neuroimmunol Neuroinflamm*, 2021, pubmed.ncbi.nlm.nih.gov/33658321/

ABNORMAL DEVELOPMENT OF THE ENTERIC NERVOUS SYSTEM

Hirschsprung's disease (HSCR) is the most common developmental abnormality of the enteric nervous system and results in neonatal distal intestinal obstruction. The 'Embryology and genetics of malformations' research team directed by Prof. Jeanne Amiel, has identified a problem with genes *ERBB3* or *ERBB2* that can cause HSCR, associated with a wide range of developmental abnormalities as well as considerable hypomobility of the entire intestinal tract making medical care and surgery very difficult.

T.L. Le et al., *J Clin Invest*, 2021, pubmed.ncbi.nlm.nih.gov/33497358/



APRIL :

LEBER'S OPTIC NEUROPATHY - THE END OF AN ENIGMA

Leber hereditary optic neuropathy (LHON) is a degenerative disease of the central fibers of the optic nerve that causes a sudden and massive decrease in visual acuity in one eye that rapidly spreads to the other. The disease is due to mutations in the mitochondrial DNA (transmitted only by the mother), whose integrity is essential to the production of energy and therefore to the survival of the cells. For many years, the scientific community questioned the existence of cases of Leber-type optic neuropathies without detectable mutations in the mitochondrial genome. However, in 2016, the Genetics in Ophthalmology research lab (LGO), headed up by Dr. Jean-Michel Rozet, identified mutations in the *NDUFS2* gene in two brothers suffering from actual Leber optic neuropathy. For the first time, a link with the DNA of the cell nucleus was considered. This hypothesis was confirmed beyond any doubt in 2021 when a team from the University of Munich – with which the LGO is affiliated – identified mutations in the nuclear gene *DNAJC30* at the origin of a large number of unresolved cases. The LGO also published findings showing mutations in a third nuclear gene, *MCAT*, in a similar-type case. These discoveries, which demonstrate the existence of nuclear Leber optic neuropathies, resolved an enigma that had long intrigued the scientific community as well as highlighting unexpected genetic heterogeneity.

L. Stenton et al., *J Clin Invest*, 2021, pubmed.ncbi.nlm.nih.gov/33465056/

Gerber et al., *Genes*, 2021, pubmed.ncbi.nlm.nih.gov/33918393/



FRIEDREICH'S ATAXIA: IDENTIFICATION OF A THERAPEUTIC MOLECULE

Dr Agnès Rötig's 'Genetics of mitochondrial diseases' research team has demonstrated how a deficiency in a mitochondrial protein - frataxin - responsible for Friedreich's ataxia, modifies the entry, transit and exit of iron in the cell. The consequences of frataxin deficiency are many and not all are understood, however the accumulation of iron in the heart and brain is certainly very harmful in this neurogenetic disease. This research has also identified a therapeutic molecule that will soon be tested in patients suffering from this disease in a phase I-II clinical trial.

F. Petit et al., *Blood*, 2021, pubmed.ncbi.nlm.nih.gov/33529321/

ANKRD17 AND INTELLECTUAL IMPAIRMENT

Mutations in this gene have been identified in patients with intellectual disabilities, especially those affecting language and sometimes associated with a cleft palate and/or increased vulnerability to infections. The team headed up by Prof. Jeanne Amiel, Director of the 'Embryology and genetics of malformations' research lab, has analyzed this neurodevelopmental disorder from a cohort of 34 individuals from 32 different families. These findings will improve diagnosis and genetic counseling for these families and provide increased hope of innovative targeted therapies.

M. Chopra et al., *Am J Hum Genet*, 2021, pubmed.ncbi.nlm.nih.gov/33909992/

USING AI TO GENERATE CELLULAR ID CARDS



Our body comprises billions of cells. Characterizing all of these extremely heterogeneous cells is crucial to understanding how they function, identifying the molecular mechanisms of genetic diseases and treating them. With the support of the French National Research Agency (ANR) as part of the French Government Investments for the Future (PIA) Program, and Christian Dior Couture, the Clinical bioinformatics research lab, headed up by Dr. Antonio Rausell, has developed a computerized method of extracting molecular signatures at individual cell level, and thus generating an identity card for each different cell within a given sample. These cellular identity cards can then be used to identify cell markers for diagnostic and prognostic ends, as well as for individual treatment programs.

A. Cortal et al., *Nat Biotechnol*, 2021, pubmed.ncbi.nlm.nih.gov/33927417/



MAY:



IPO8

This is the name of the gene identified by Dr. Nadine Cerf-Bensussan's team, in liaison with research labs in seven countries. This gene is responsible for connective tissue dysplasia, a group of pathologies that affect vessels, the skeletal structure and the skin. The most feared of these disorders is the occurrence of aortic aneurysms. Twelve patients affected by this mutation suffered from cardiovascular impairment, joint hyperlaxity, and defective control of the immune system. Several also suffered from intestinal inflammation. All shared a mutation of gene *IPO8* that disrupts the TGF- β signaling pathway, essential for the development and functioning of connective tissue cells and regulation of the immune system, which accounts for this clinical overview. This discovery, concerning a rare disease, could provide a better understanding of more common vascular and immune diseases.

A. Ziegler et al., *Am J Hum Genet*, 2021, pubmed.ncbi.nlm.nih.gov/34010604/





EPSTEIN-BARR VIRUS: AN INVENTORY OF ATYPICAL INFECTIONS

Epstein-Barr virus (EBV) is one of the most common viral infections in humans (90-95% of the adult population infected are asymptomatic carriers). Consequently, innate immune or primary immunodeficiency defects that give a predisposition to severe EBV infections provide interesting examples for deciphering the molecular and cellular components that affect the immune control of infected cells. In a review of scientific literature, Dr. Sylvain Latour, Director of the lab that researches 'Lymphocyte activation and sensitivity to Epstein-Barr virus', focused on recent knowledge and concepts concerning 'atypical' infections, when EBV penetrates T (killer) and NK (natural killer) immune cells, instead of typical B lymphocyte infections.

B. Fournier & S. Latour, Curr Opin Immunol, 2021, pubmed.ncbi.nlm.nih.gov/33989894/

A HIGHLY PROMISING MOLECULAR COCKTAIL

Mutations in genes FGFR3 and NPRB lead respectively to achondroplasia (the primary cause of dwarfism) and Acromesomelic dysplasia, Maroteaux type (AMDM). Dr. Laurence Legeai-Mallet's team had previously shown that an NPRB agonist molecule known as BMN-111 - or vosoritide - boosts bone growth in mice. In a new ex-vivo study, her team demonstrated that this treatment, combined with another molecule called LB-100 (a phosphatase inhibitor), increases bone length and cartilage and proliferative growth plate surface, more than just vosoritide on its own. At the same time, working with Dr. Lincoln Potter, the team demonstrated that

crossing mice with NPR-B resistance to dephosphorylation, with mice suffering from achondroplasia actually corrected dwarfism. These are two very hopeful findings.

L. C. Shuhaibar et al., JCI Insight, 2021, pubmed.ncbi.nlm.nih.gov/33986191/

B. M Wagner et al., JCI Insight, 2021, pubmed.ncbi.nlm.nih.gov/33784257/

DISRUPTED NEURONAL MIGRATION

Reelin is a protein secreted by certain neurons that controls several stages of cerebral cortex development, particularly neuronal migration, a phenomenon essential for structuring neuronal networks. Until now, only recessive mutations of reelin (RELN) gene coding have been associated with cortical malformations in humans and none has been characterized functionally. However, the 'Genetics and development of the cerebral cortex' lab headed up by Dr. Alessandra Pierani, has identified new missense variants in the RELN gene in patients with a range of neuronal migration disorders. Researchers characterized the consequences of these mutations using in vitro and in vivo approaches, and demonstrated that the behavior of the mutant proteins predicts the severity of cortical malformations and provides valuable information concerning the pathogenesis of these disorders. This is the first time that the pathogenicity of RELN mutations has been demonstrated, revealing a strong genotype-phenotype correlation.

M. Riva et al., bioRxiv, 2021, doi.org/10.1101/2021.05.25.445586

JUNE:

GETTING TO THE HEART OF HEART DISEASE

Congenital heart disease is the most common congenital disorder and the main cause of death in both the embryonic stage and during the first year of life. In 80% of cases, the genetic cause is still unknown, however, advances in genetics, imaging and omics have led to the discovery of new heart formation and malformation mechanisms in animal models. In a review of scientific literature, Dr. Sigolène Meilhac, Director of the 'Heart morphogenesis' research lab, and Dr. Lucile Houyel, a cardiopediatrician at the Necker Hospital for sick children, summarize the latest knowledge in this area and the prospects for both basic and clinical research.

L. Houyel & S. Meilhac, Annu Rev Genomics Hum Genet, 2021, pubmed.ncbi.nlm.nih.gov/34061573/



OPTIMIZING BLOOD STEM CELL TRANSPLANTS

The team around Dr. Isabelle André, Director of the 'Human lymphohematopoiesis' lab, has developed a new cell culture process that significantly reduces the renewal time of T lymphocytes from blood (or haematopoietic) stem cells.

This should reduce the period of immune vulnerability in patients receiving a bone marrow transplant and help avoid problems with infections. Two clinical trials piloted by the AP-HP (Paris public hospitals authority) to test this approach have been launched: the first with children suffering from severe hereditary immunodeficiency (i.e., Bubble baby disease), and the second with adults suffering from acute myeloid leukemia. A third trial is planned for the United States. It is being coordinated by the 'Smart Immune' startup, created in 2017 within Institut Imagine.

R. Devi. Moirangthem et al., Cell Mol Immunol, 2021, pubmed.ncbi.nlm.nih.gov/34117371/



JULY:

A NEW ENCEPHALOPATHY

The team headed up by Dr. Vincent Cantagrel, Director of the 'Developmental brain disorders' research lab, has conducted a collaborative study of the genetics of a cohort of Egyptian patients with an encephalopathy affecting the cerebellum and cerebral atrophy of unknown origin. This research has enabled the team to identify a new molecular cause for many patients, in particular defects in the make-up of the GPI anchor, a structure that allows proteins to be attached to the plasma membrane. Part of this work has demonstrated that this defect is at the origin of a new blood group identified in liaison with the research team of Dr. Slim Azouzi at Institut National de la Transfusion Sanguine.

R. Duval et al., Blood, 2021, pubmed.ncbi.nlm.nih.gov/33763700/



TREE-MAN SYNDROME

A large part of the population are carriers of human papillomaviruses (HPVs), particularly cutaneous papillomaviruses, which generally cause warts or local benign lesions. However, very few patients develop severe forms of these viral diseases, which include 'tree-man' syndrome. This severely disabling disease is accompanied by an aggressive outbreak of cutaneous horns that cannot be treated effectively by surgery. Dr. Vivien Béziat, who is part of the Human genetics of infectious diseases research lab directed by Prof. Jean-Laurent Casanova and Dr. Laurent Abel, has identified for the first time a genetic cause of this syndrome, as part of a joint international effort.

V. Béziat et al. Cell, 2021, pubmed.ncbi.nlm.nih.gov/34214472/

POST-SURGICAL MUTISM

Some children are temporarily unable to speak following surgery to resect a medulloblastoma in the cerebellum. Pediatric cerebellar mutism syndrome is still poorly understood. The Image@Imagine team led by Prof. Nathalie Boddaert has shown that children who develop this complication are significantly more likely to show an abnormal MRI response (T2-weighted hyperintensities) in the dentate nucleus of the cerebellum and a significant decrease in postoperative blood flow in two areas of the brain involved in the motor functions of speech.

J. Boisgontier et al., J Cereb Blood Flow Metab, pubmed.ncbi.nlm.nih.gov/34259072/



AUGUST:

08

NEW VECTORS TO COMBAT SICKLE CELL DISEASE



Sickle cell disease is a blood disorder caused by a mutation in the gene for globine β , a protein of hemoglobin.

At present, the only curative treatment is a bone marrow transplant. In the absence of a donor, another approach is gene therapy using lentiviral vectors to deliver a new healthy gene into patients' stem cells. However, this technology is very expensive and effectiveness varies greatly between patients. In this context, Dr. Annarita Miccio's team has developed innovative approaches to optimize the healthy gene expression in order to produce more therapeutic hemoglobin while at the same time 'deactivating' the mutated gene using CRISPR-Cas9 'molecular scissors' technology. The team was able to test several of these new vectors in vitro. And the result? At a given dose, they are more effective than the vectors currently used in clinics. These are highly promising basic and preliminary findings that need to be confirmed *in vivo*.

S. Ramadier et al., *Molecular Therapy*, pubmed.ncbi.nlm.nih.gov/34418541/

COMPENSATORY MUTATIONS



Certain mutations that appear spontaneously over a lifetime can counteract the effects of genetic diseases.

For Dr. Patrick Revy, Co-director of the 'Dynamics of the genome in the immune system' lab at Institut *Imagine*, these 'compensatory somatic mutations' are more common than we think. In a study published in *Nature Communications*, his team identified this type of mutation in Shwachman-Diamond syndrome, a genetic disease that leads to a deficiency of certain white blood cells, and analyzed its effects at molecular level.

S. Tan, L. Kermasson et al., *Nat Commun*, 2021, pubmed.ncbi.nlm.nih.gov/34413298/

SEPTEMBER:

09

SURGERY: THE PROMISES OF 3D MODELING

Prof. Sabine Sarnacki and her team have been studying the impact of minimally-invasive and robot-assisted surgery on benign and malignant tumors in children in a study that included the largest cohort of patients in this domain. And the outcome? The precision and dexterity of the manipulator controlled remotely by the surgeon as well as the 3D images provided by the on-board high-definition binocular camera have made it possible to broaden the scope of this technology. Moreover, thanks to applications developed in the IMAG2 laboratory affiliated to Institut *Imagine*, a significant number of patients have been able to benefit from 3D modeling using previous-generation images taken before the operation. This modeling is generated quasi automatically using AI techniques that make it possible to prepare for surgery more effectively and to explain more clearly to the child and their family the nature of the operation and what is at stake. Going forward, the laboratory's aim is to set up GPS-style real-time guidance during the operation by incorporating these images into the surgical robot console's 3D images.

T. Blanc et al., *Ann Surg Oncol*, pubmed.ncbi.nlm.nih.gov/34523002/

WORKING TOWARDS PRECISION MEDICINE FOR NETHERTON SYNDROME

Netherton syndrome (NS) is a rare genetic skin disease caused by loss-of-function mutations in the *SPINK5* gene. Those affected have a severely depleted skin barrier causing inflammatory skin lesions and scaling. Depending on the nature of these lesions, we may distinguish between two clinical forms of NS. By combining several molecular profiling methods (transcriptomic and proteomic) on a cohort of 13 patients, the team led by Prof. Alain Hovnanian, Director of the 'Genetic skin diseases' research lab, managed to analyze the shared features and subtle differences between these two forms. They confirmed that interleukins 17 and 36 (inflammatory molecules) are the main molecular signaling pathways in both subtypes, while the Type 1 interferon pathway and allergic responses differ. These findings made it possible to identify new therapeutic targets and pave the way for precision medicine for Netherton syndrome.

C. Barbieux et al., *J Allergy Clin Immunol*, 2021, pubmed.ncbi.nlm.nih.gov/34543653/

OCTOBER:

10

UNDERSTANDING EWING SARCOMA

Dr. Erika Brunet's group within the 'Dynamics of the genome in the immune system' lab, led by Dr. Patrick Revy and Dr. Jean-Pierre de Villartay, has developed the very first human cell model reproducing genetic aberrations known as 'chromosomal translocations' that cause Ewing's sarcoma, a malignant bone tumor that mainly affects children and adolescents. This model, developed using CRISPR-Cas9 technology, has made it possible to identify the phenotypic, transcriptomic and epigenetic characteristics of the associated tumors as well as the successive stages of tumor formation both in vitro and *in vivo*.

A. Sole et al., *Cancer Research*, 2021, pubmed.ncbi.nlm.nih.gov/34341072/



AN UNSUSPECTED LINK

The Neurogenetics and neuroinflammation research team headed up by Prof. Yanick Crow, together with teams from the Necker Public Hospital for sick children in Paris, has identified mutations in the *ATAD3A* gene in patients suffering from a rare skin condition - scleroderma - in addition to a neurological disease. These mutations trigger the release of mitochondrial DNA into the cytoplasm, leading to accumulation of type I interferons in the blood and in skin cells known as fibroblasts. The team has therefore identified a new link between two ostensibly distinct classes of diseases, namely mitochondrial diseases and interferonopathies.

A. Lepelley et al., *J Exp Med*, 2021, pubmed.ncbi.nlm.nih.gov/34387651/

11

NOVEMBER:

 GENETICS OF VIRAL INFECTIONS

Exposure to a virus triggers very different responses from one person to another. In a review of scientific research published in *Science*, Dr. Laurent Abel and Prof. Jean-Laurent Casanova, co-directors of the Human genetics of infectious diseases research lab, take stock of more than 20 years of research into their pioneering hypothesis of a genetic link to such 'inter-individual' variability.

J.L. Casanova & L. Abel, *Science*, 2021, pubmed.ncbi.nlm.nih.gov/34822298/

 TRANSPLANTS: A VERY PROMISING CANDIDATE

Over the past decade, a new class of drugs has revolutionized cancer treatment, namely Chimeric Antigen Receptor (CAR) T-cells.

These are immune cells (T lymphocytes) genetically modified to destroy cancerous cells. This approach could ultimately be extended to another field of application – organ transplants and autoimmune diseases – and researchers are currently developing 'regulatory' CAR-T cells (CAR-Treg) for this very purpose. A bit like orchestra maestros, these cells can selectively control the immune response to avoid rejection, while preserving anti-infectious and anti-tumor responses. An entire field of research focuses on finding the best 'recipe' for making them more stable. Dr. Julien Zuber's team, which is part of the Human lymphohaematopoiesis research lab directed by Dr. Isabelle André, has made significant progress by identifying one of the key ingredients in this recipe. By studying different chimeric receptor designs, the researchers have demonstrated that the most stable and appropriate design for future clinical trials is that present in the CD28 receptor.

B. Lamarthée et al., *Nature Communications*, 2021, pubmed.ncbi.nlm.nih.gov/34750385/

12

DECEMBER:

 MASTOCYTOSIS AND CANCER

Mastocytosis is an abnormal proliferation of mast cells (cells of the innate immune system) in tissues. It is usually cutaneous but systemic forms exist, including a category of aggressive forms such as mast cell leukemia and mast cell sarcoma. In 85% of cases, a mutation is detected in the *KIT* gene of pathological mast cells, however, this mutation alone does not account for the abnormal proliferation of the cells, suggesting the involvement of other causes (genes). By analyzing extremely rare cases of children suffering from both aggressive mastocytosis and Greig syndrome – a polymalformative syndrome characterized by a large head circumference and the presence of six fingers – the team of Dr. Leïla Maouche-Chrétien, from the Hematological disorders research lab directed by Prof. Olivier Hermine, has demonstrated the involvement of the 'hedgehog' pathway in mastocytosis in these children. In particular, the researchers – including dermatologist Laura Polivka – have demonstrated that the mutation in the *GLI3* gene responsible for the polymalformative syndrome, works with the cKIT mutation to trigger abnormal mast cell proliferation. Using a model of aggressive mastocytosis present in a mouse, the researchers demonstrated the efficacy of a treatment that blocks proliferation of pathological mast cells and boosts the animal's chances of survival. This highly promising treatment strategy could ultimately benefit a much larger number of patients suffering from aggressive mastocytosis.

L. Polivka et al., *Blood*, 2021, pubmed.ncbi.nlm.nih.gov/34424959/




CONTINUING THE FIGHT AGAINST COVID-19

For the second consecutive year, the Covid-19 pandemic has focused the attention of researchers at Institut *Imagine*, who have leveraged all of their scientific knowledge and expertise to gain a better understanding of the genetic, immunological and immune system aspects of the virus. Here is a brief update on the progress made in 2021.

 DISCOVERY OF A MOLECULAR PROFILE FOR PEDIATRIC MYOCARDITIS

Certain children infected with SARS-Cov-2 develop severe inflammations after four to six weeks accompanied by a variety of symptoms: fever, gastric pain, skin rashes, etc. In about 70% of cases, this 'multi-systemic' inflammatory syndrome reaches the myocardium, the muscle that controls heart contractions. How can this be explained? In a study published in *MED*, the teams of Dr. Mickaël Ménager and Dr. Frédéric Rieux-Laucat, respectively directors of the 'Inflammatory responses and transcriptomic networks in diseases' and 'Immunogenetics of pediatric autoimmune diseases' research labs at Institut *Imagine*, in liaison with doctors from the AP-HP (Paris public hospitals authority) and researchers from the Pasteur Institute, analyzed the blood of a cohort of 56 young patients at the Necker Public Hospital for sick children in Paris. They identified abnormal expression among several genes associated with severe forms of post-Covid myocarditis. This molecular profile could in time make it possible to identify children at risk of developing this rare form of cardiac inflammation.

C. de Cevins et al., *Med*, 2021, pubmed.ncbi.nlm.nih.gov/34414385/

 AN EXPLANATION FOR MORE THAN 20% OF SEVERE FORMS OF COVID-19

The consequences of Sars-Cov-2 are infinitely variable from one person to another. While most infected individuals are minimally symptomatic or asymptomatic, some develop severe or even critical forms of the disease along with pneumonia requiring a stint in intensive care. How can these disparities be explained? Two studies published in *Science Immunology* [1] [2] by teams from the Human genetics of infectious diseases research lab headed up by Prof. Jean Laurent Casanova and Dr. Laurent Abel, have shed considerable light on this question. They point up genetic and immunological abnormalities which account for nearly 25% of severe forms of Covid-19. All of these abnormalities hamper the immunity controlled by Type 1 interferon, the first immunological barrier against viral infections.

T. Asano et al, *Science Immunology*, 2021, pubmed.ncbi.nlm.nih.gov/34413140/

P. Bastard et al., *Science Immunology*, 2021, pubmed.ncbi.nlm.nih.gov/34413139/



INNOVATING AND CURING

'Institut Imagine rallies all stakeholders and gets them working at the same time and in the same places on behalf of sick children and their families in search of answers and treatments. It is this combination of scientific, clinical, medical and innovative expertise, at the juncture of excellent scientific research and human and innovative pediatric and adult medicine that is harnessed for the benefit of patients.'

Prof. Olivier Hermine, Head of the WP4 program,
'Developing innovative therapies', run by Institut *Imagine*
- Necker Public Hospital for sick children

At Institut *Imagine*, everything starts and ends with the patient. Designed as a single model that brings doctors and researchers together with patients, working in a virtuous loop, the Institute harnesses 28 research teams, 18 leading-edge tech platforms, 31 reference centers for rare diseases, 8 clinical research units and 2 clinical investigation centers affiliated to Necker, Cochin and HEGP public hospitals (run by AP-HP, the Paris public hospitals authority). Doctors, researchers, engineers and technicians work hand in hand to improve knowledge of genetic diseases and how they are cared for and to develop new treatments. Considerable progress was made in 2021. This could not have been achieved without this research-care continuum or cooperation with our partners in academia, industry, start-ups and in biotech.

CLINICAL RESEARCH: FROM BASIC RESEARCH TO TREATMENT

By functioning as an open loop, Institut *Imagine* makes it easier to go further, faster. Clinical observation and research provide a better understanding of the causes of diseases and how they work and ultimately, to make diagnoses and move towards future treatments.

Clinical research subsequently makes it possible to deploy these scientific innovations and new diagnostic and therapeutic approaches, improving patient care in the process.

'Genetics cannot do without clinical research. The more research there is into genetics, the higher the quality of clinical research required – and not the other way around. Institut Imagine has been specifically designed to accelerate this transition from the clinical lab to research and vice versa.'

Stanislas Lyonnet,
Director, Institut *Imagine*.

CLINICAL RESEARCH IN 2021 – IN FIGURES

- Over **500** clinical trials in progress;
- By ramping up its activities, *Imagine* has been able to provide support to **90** institutional or industrial promotion projects and include over **250** patients in 2021
- Among the **90** studies supported by the Institute's clinical research team:
 - 15** do not involve human beings (i.e., outside the scope of the Jardé Law) and
 - 72** actually involve human beings (*RIPH1* to *RIPH3*), including **44** intervention studies (*RIPH1* and *RIPH2*) and **28** non-intervention studies (*RIPH3*)*.

*There are two categories of studies involving human beings (*RIPH*): intervention and non-intervention studies. An intervention study comprises a non-risk-free intervention on individuals outside the scope of usual care. It may involve varying degrees of risk (from blood sampling to surgery). A non-intervention study (*RIPH3*) does not change the patient's care program and does not involve risk. A study that does not involve human beings (i.e., outside the scope of the Jardé Law) uses existing data for a purpose other than care with or without existing biological elements.

PROMOTING CLINICAL TRIALS

Once laboratories have gathered all necessary proofs of concept and preclinical studies on potential treatments or methods of diagnosis, it is time for clinical development to begin. Clinical research comprises scientific studies carried out on human beings for the purpose of developing biological or medical knowledge. It involves monitoring patients or healthy volunteers.

To accelerate this process, the Institute deploys considerable human resources to help promote research. The team consists of project managers in charge of getting trials up and running, Clinical Research Coordinators and Clinical Research Technicians, working with the teams in the reference centers for rare diseases (*CRMRS*) and mobile clinical research nurses. They develop clinical research activities, patient inclusion programs and dissemination of best practices as well as personalized care paths in liaison with the *CRMRS*.

The clinical research team provides support to the reference centers for rare diseases and the clinical departments across Institut *Imagine*'s clinical research brief. In 2021, *Imagine* provided comprehensive support to the researchers and clinicians of its founding members, AP-HP (Paris public hospitals authority), Inserm and Université Paris Cité. For example, 15 of Institut *Imagine*'s 31 reference centers

for rare diseases have benefited from this program.

In total, in 2021 the Institute's acceleration program provided support to 90 institutional or industrial promotion projects that include more than 250 patients. They included ATRACtion, a program to develop diagnostic, prognostic and therapeutic applications for patients suffering from autoimmune diseases and inflammation. Inclusion in this Inserm-backed program began in December 2021 and it leverages all of the clinical investigation resources deployed by Institut *Imagine*.

MAIN FOCUSES OF CLINICAL TRIALS IN 2021

- Intellectual impairment, particularly via the national DEFIDIAG project, in which *Imagine* is one of the key players
- Metabolic disorders
- Rare skin diseases
- Kidney diseases
- Developmental disorders
- Hematology

In 2020, Institut *Imagine* and Necker Public Hospital for sick children put out a joint call for projects to pool donor funding for the benefit of the reference centers for rare diseases located on the Necker campus. To be eligible for consideration, the project must involve medical teams and patient associations.

The call for projects is designed to encourage collaborative and multi-disciplinary projects in the field of clinical research applied to rare diseases. In 2021, the jury convened and selected two projects.



A FIRST CHILD SUFFERING FROM ACHONDROPLASIA BENEFITS FROM A NOVEL TREATMENT

On March 30, 2021, the first French child suffering from achondroplasia, the most common form of dwarfism, received *infigratinib*, an experimental drug discovered at Institut *Imagine* and currently being developed by QED Therapeutics at Necker Public Hospital for sick children, as part of an international clinical trial.

Back in 1994, **Dr. Laurence Legeai-Mallet**, who heads up one of *Imagine*'s research labs, jointly discovered *FGFR3*, the gene responsible for the disease. Since then, herself and her team have developed appropriate trial models to characterize the pathophysiological pathways, test different drug candidates, and patent the use of *infigratinib* for achondroplasia.

The investor BridgeBio was immediately interested in the findings and acquired the rights to the patent. It set up QED Therapeutics to develop the drug and begin the first international clinical trial. *Infigratinib* was administered for the first time in July 2020 in Melbourne, Australia and in March 2021, trials began in France at Necker Public Hospital for sick children. They are being overseen by teams from the hospital and Institut *Imagine*, including Dr. Kim-Hanh Le Quan Sang, Dr. Geneviève Baujat and Prof. Valérie Cormier-Daire.

As Laurence Legeai-Mallet explains, 'we hope to use this treatment to correct this unique genetic mutation – in other words, to partially correct elongated long bones and defects in the growth plate'.



REFERENCE CENTERS FOR RARE DISEASES (CRM) AT THE HEART OF PATIENT CARE

When dealing with a genetic disease, the expertise of doctors who have already been confronted with the same – often rare – pathology, is absolutely essential. The Reference Centers for Rare Diseases have been designed exactly for this purpose – to organize and structure care networks. A reference center harnesses all of the energy of highly specialized medical teams with proven expertise in a rare disease or group of rare diseases, covering para-medical, psychological, medico-social, educational and social skills.

In 2021, 29 reference centers for rare diseases at Necker Public Hospital for sick children were affiliated to Institut *Imagine*, and since 2021, two reference centers located at Cochin and HEGP public hospitals have joined *Imagine*.

6 NEW REFERENCE CENTERS FOR RARE DISEASES OFFICIALLY AFFILIATED TO INSTITUT *IMAGINE* IN JANUARY 2021

- Cardiomyopathy and hereditary cardiac rhythm disorders, HEGP – Albert Hagège
- Cardiomyopathy in neuromuscular diseases, Cochin – Karim Wahbi
- Hereditary heart disease North/East France/Paris Region – Damien Bonnet
- Thrombotic microangiopathy – Aude Servais
- Idiopathic nephrotic syndrome – Bertrand Knebelmann and Olivia Boyer
- Neuromuscular diseases North/East France/Paris Region – Isabelle Desguerre



REFERENCE CENTERS FOR RARE DISEASES RESEARCH AND CARE ACCELERATORS

NEPHROLOGY

- ▶ **L. Heidet**
Hereditary kidney disease in children and adults (MARHEA)
- ▶ **A. Servais**
Thrombotic microangiopathies (CNR-MAT)
- ▶ **B. Knebelmann & O. Boyer**
Idiopathic nephrotic syndrome (INS)

NEURODEVELOPMENT

- ▶ **N. Bahi-Buisson**
Rare forms of intellectual impairment – multiple disabilities
- ▶ **D. Brémond-Gignac**
Rare eye diseases (OPHTARA)
- ▶ **JP Bonnefont**
Mitochondrial diseases in adults and children (CARAMMEL)
- ▶ **P. De Lonlay**
Hereditary metabolic disorders
- ▶ **I. Desguerre**
Neuromuscular diseases North/East France/Paris Region
- ▶ **R. Nabbout**
Rare forms of epilepsy (CRéER)
- ▶ **M. Rio**
Rare forms of intellectual impairment

HEMATOLOGY

- ▶ **A. Harroche**
Pediatric hemophilia
- ▶ **O. Hermine**
Mastocytosis (CEREMAST)
- ▶ **M. de Montalembert**
Major sickle cell syndromes, thalassemias and other rare red blood cell and erythropoiesis disorders

IMMUNOLOGY-INFECTOLOGY-GASTROLOGY

- ▶ **A. Fischer & N. Malhaoui**
Hereditary immunodeficiencies (CEREDIH)
- ▶ **F. Ruemmele**
Rare digestive tract diseases (MARDI)
- ▶ **P. Quartier dit Maire**
Inflammatory rheumatism and rare systemic autoimmune diseases in children (RAISE)

DEVELOPMENT & CARDIOLOGY

- ▶ **V. Abadie**
Pierre Robin syndrome and congenital sucking and swallowing disorders (SPRATON)
- ▶ **J. Amiel**
Developmental abnormalities and malformation syndromes
- ▶ **S. James**
Rare vertebral and medullary malformations
- ▶ **G. Paternoster**
Craniosynostoses and craniofacial malformations

- ▶ **D. Bonnet**
Complex congenital heart defects (M3C)
- ▶ **D. Bonnet**
Cardiomyopathies and hereditary cardiac rhythm disorders
- ▶ **C. Bodemer**
Rare skin and mucous membrane diseases of genetic origin (MAGEC)
- ▶ **V. Cormier-Daire**
Constitutional bone diseases (MOC)
- ▶ **C. Crétolle**
Rare anorectal and pelvic disorders (MAREP)
- ▶ **F. Denoyelle**
Rare ENT malformations (MALO)
- ▶ **A. Hagège**
Cardiomyopathy and hereditary cardiac rhythm disorders, HEGP
- ▶ **S. Marlin**
Genetic deafness
- ▶ **A. Picard**
Clefts and facial malformations (MAFACE)
- ▶ **M. Polak**
Rare gynecological pathologies (PGR)
- ▶ **K. Wahbi**
Cardiomyopathy in neuromuscular diseases, Cochin

2 CLINICAL INVESTIGATION CENTERS (CIC)

- ▶ **M. Cavazzana**
Biotherapies (CIC-BT)
- ▶ **JM. Tréluyer**
Multi-thematic Mother and Child Unit (CIC)

8 AFFILIATED CLINICAL DEPARTMENTS

- ▶ **P. Quartier dit Maire**
Pediatric immunology, hematology and rheumatology
- ▶ **O. Hermine**
Adult hematology
- ▶ **M. Cavazzana**
Innovative therapies
- ▶ Federation of medical genetics
- ▶ **D. Anglicheau**
Adult kidney transplants
- ▶ **A. Burgun**
Medical Informatics
- ▶ **R. Salomon**
Pediatric nephrology
- ▶ **O. Lortholary**
Infectious and tropical diseases

FROM DISCOVERY TO INNOVATION: SHOWCASING OUR RESEARCH

Since its creation, Institut *Imagine*, with the help of its Innovation and Technology Transfer Department, currently headed up by H el ene Chautard, has demonstrated its ability to accelerate translational and clinical research and showcase these developments to the socio-economic partners.

In 2021, Institut *Imagine* greatly increased the number of its corporate partnerships, coordinated major research projects involving both academia and private companies, and supported the creation of start-ups.

RESEARCH CAPITALIZATION IN 2021 – IN FIGURES

- **15** patents filed within Institut *Imagine*. The patent portfolio covers a wide range of applications comprising **52** active patent families
- **2** operating licenses signed
- **23** new R&D partnership agreements signed
- **€1.2 MILLION** worth of revenue generated by industrial contracts signed in 2021 and reinvested in research and care activities.
- **3** new projects integrated into 'Springboard', the first accelerator to provide start-ups focused on genetic diseases with financial advice and expertise, bringing the total number of projects supported to 6. These projects focus on developing serotonin derivatives in sickle cell disease, repositioning molecules for pain management, and developing a gene therapy to treat leukemia. Since 2012, nine start-ups have been created at the Institute, including six resulting directly from *Imagine's* research work and 3 fast-tracked via the *Bioentrepreneurs* program.
- More than **140** therapeutic and diagnostic solutions resulting directly from the Institute's research.

A GROWING NUMBER OF RESEARCH PARTNERSHIPS WITH BUSINESS

In 2021, Fondation *Imagine* managed to generate strong partnership momentum with the pharma industry and innovative healthcare companies and start-ups. *Imagine's* research partnership activity has doubled since its creation and this growth was apparent in 2021 with a number of new industrial partnerships.



FLAGSHIP PARTNERSHIPS IN 2021 FOCUSED ON THE FOLLOWING AREAS:

- **Innovative** gene and cell **therapies**, particularly for blood diseases, immune deficiencies and metabolic disorders
- Targeted **molecular therapies** for lymphomas and lymphoproliferative syndromes
- Treatment of constitutional bone diseases with **small molecules**
- **Screening and repositioning molecules**, particularly for ciliopathies and developmental anomalies
- **Digital health** and the high hopes raised by the possibility that digital twins will be able to treat certain rare diseases

In the field of innovative therapies, Institut *Imagine* works with **Collectis**, hosted in its Lab-in-Labs – a platform dedicated to partners in the pharmaceutical sector. Collectis is developing Talen, a highly accurate and versatile genome editing technology. In May 2021, it launched Heal, a new hematopoietic stem cell-based gene therapy platform that leverages Talen technology to perform highly effective gene correction in haematopoietic stem and progenitor cells for diseases such as sickle cell disease, lysosomal diseases and primary immunodeficiency. Dr. Annarita Miccio's team at Institut *Imagine* is liaising with Collectis to test this technology on sickle cell disease.

Institut *Imagine* has also stepped up its partnership with **TreeFrog Therapeutics**, a biotech company developing a disruptive technique for producing safer and more affordable cell-based therapies: C-StemTM, a high-throughput encapsulated cell technology that makes it possible to grow and differentiate stem cells in industrial bioreactors on a large-scale. *Imagine* is part of the QC-Stem consortium, which brings together TreeFrog Therapeutics and experts from the Harvard Stem Cell Institute and the Dana-Farber Cancer Institute in Boston (USA), as well as from the FBRI in Kobe (Japan) to evaluate the quality of stem cells produced using this technology. With this objective in mind, *Imagine* is hosting a PhD student from TreeFrog Therapeutics who is doing a thesis as part of a CIFRE agreement (research-based industrial training) on 'Developing bioproduction methods for cell therapy based on pluripotent cells using encapsulated cell technology'.

Again in the field of cell therapy, Institut *Imagine* has forged a partnership with biotech **Smart Immune**, a start-up created in 2017 at the Institute by Karine Rossignol, Dr. Isabelle Andr e and Prof. Marina Cavazzana to accelerate the development of innova-

tive treatments, particularly with a view to reconstituting the immune system following a transplant.

The research team headed up by Isabelle Andr e has developed a new cell therapy procedure with the aim of reducing the period of immune vulnerability following a transplant and avoiding rejection. Two clinical trials piloted by the AP-HP (Paris public hospitals authority) to test this approach have been launched, the first with children suffering from severe hereditary immunodeficiency (i.e., Bubble baby disease), and the second with adults suffering from acute myeloid leukemia. A third trial will be piloted by Smart Immune in the United States. Moreover, new partnerships have been forged between Isabelle Andr e's team and biotech on the development and pre-clinical validation of cell therapy protocols.

Lastly, in 2021, Institut *Imagine* entered into an agreement with **Moderna** to develop a new therapeutic approach based on RNA messenger for an extremely rare metabolic disease, leukinosis. Teams from the Institute and Necker Public Hospital for sick children, with the support of Prof. Manuel Schiff and Dr. Cl ement Pontoizeau, are testing these Moderna-produced RNAs on animals to specifically target two genes responsible for the disease, with the aim of developing multiple complementary treatments.

Other partnerships were created or developed in 2021, including those with **QED Therapeutics** in the field of achondroplasia (see page 32), **STEP Pharma** in immuno-oncology, **Cerba HealthCare** (see page 39) to develop predisposition testing for severe forms of Covid-19, and start-ups **AtmosR** and **Medetia**, both hosted at the Institute, working on Central hypoventilation syndrome. After the discovery of the gene responsible by Prof. Jeanne Amiel's team nearly twenty years ago, the two start-ups and Institut *Imagine* have teamed up to identify the most promising molecules for future treatment of this rare and very serious disease.

COORDINATING CROSS-DISCIPLINARY PROJECTS

There has also been very strong momentum in publicly-funded projects with industrial partners. Institut *Imagine*'s teams were keenly focused on all of the main funding opportunities in 2021, at regional, national and European level. This dynamic, together with the Institute's tried and tested public-private financing model, have enabled it to successfully bid for major projects and to coordinate cross-disciplinary projects that have a real impact on access to research and care.

In 2021, *Imagine* was a successful bidder in the fifth wave of calls for *RHU* projects (i.e., university-medical research) as part of the Investments for the Future (PIA) Program coordinated by the French National Research Agency (ANR) for the COVIFERON project headed up by Prof. Jean-Laurent Casanova.

The Institute had already coordinated two *RHU* projects: *RHU4*, secured at the end of 2019 with the *ATRACTION* project, led by Dr. Frédéric Rieux-Laucat, brings together eleven industrial and academic partners, including Sanofi and Ariana Pharma. It aims to develop precision medicine for patients suffering from autoimmune and inflammatory disorders associated with primary immunodeficiency. The consortium agreement was signed in 2021. *RHU3*, the *C'IL-LICO* project headed up by Prof. Stanislas Lyonnet, brings together a consortium of academic and industrial partners to develop innovative approaches to diagnosis, prognosis and individual treatment programs for ciliopathies with renal impairment. The ANR interim report highlights the consortium's scientific results, including the *Medetia* start-up hosted at Institut *Imagine*, which emerged from this partnership and is in the full development phase.

'Institut Imagine is now the only University-Medical Institute coordinating three RHU projects and closely involved in two others (IRIS and COSY)'

Prof. Stanislas Lyonnet,
Director, Institut *Imagine*



COVIFERON: UNDERSTANDING, PREVENTING AND TREATING SEVERE FORMS OF COVID-19

'*COVIFERON*', selected in December 2021 following the *RHU5* call for projects, is coordinated by Prof. Jean-Laurent Casanova, co-director with Dr. Laurent Abel of the 'Human genetics of infectious diseases' research lab at Institut *Imagine* and Rockefeller University in New York, in liaison with both private and academic partners.

In 2020 and 2021, the teams demonstrated that around a quarter of severe forms of Covid-19 are due to immunological or genetic defects leading to a malfunction of Type 1 interferon, the first immunological barrier against viral infections. The bulk of these defects are related to the abnormally high presence of autoantibodies directed against Type 1 IFNs that neutralize their action. This research (see page 27) forms the basis of the program.

It has four focuses:

- Deciphering the genetic and immunological bases of the different clinical forms of Covid-19 using leading-edge genetic and immunological approaches,
- Developing ready-to-use diagnostic tests for accurate and large-scale detection of autoantibodies against Type 1 IFNs, in order to rapidly assess the risk of severe illness,

- Promoting the use of these tests in blood transfusions to assess the presence of these autoantibodies in blood donors,
- Proposing new preventive treatments.

The program has secured funding of **€9,988,289**.

The partners: Inserm, Université Paris Cité, Institut Pasteur, Hospices civils de Lyon (HCL), Centre International de Recherche en Infectiologie (CIRI), Université Paris Est Créteil (UPEC), Établissement Français du Sang, Cerba Health-Care, bioMérieux, Quanterix. With the help of prestigious AP-HP (Paris public hospitals authority) cohorts in this area.



To give a boost to cross-disciplinary projects, Institut *Imagine* has set up an **internal funding process, the Cross-Labs program**. The projects already funded have brought together research teams, platforms, Reference Centers for Rare Diseases, and public and private partners. The pilot model was the MSD Chair on 'DEVO-Decode' non-coding DNA, comprising eight labs, eight reference centers and eight platforms. They are provided with support in their first years of experimentation to reach proof of concept within three years. In doing so, the program creates the leverage needed to attract new partners and financial backers, and encourages the development of larger-scale projects. To take an example, the ATRACtion project was initially set up as a Cross-Labs project before being developed on a European scale within the RHU4 framework. The Cross-Labs program is crucial to developing Institut *Imagine*'s innovation and value creation ecosystem and it has facilitated disruptive, high-impact partnerships. Since the program was created in 2017, five projects have been funded, involving 14 research labs, 7 reference centers and a dozen platforms, four of which have culminated in larger projects. A new call for proposals went out in November 2021.

HELPING INNOVATIVE PROJECTS TO GET OFF THE GROUND AND SUPPORTING START-UPS

To boost the most innovative projects, Institut *Imagine* has set up an internal financing and seed funding process as well as partnerships with other research institutes.

In 2021, three new start-up projects were selected by the Scientific and Investment Committee of **Springboard, the first accelerator to provide start-ups focused on genetic diseases with financial advice and expertise**. Springboard was launched in 2020 by Institut *Imagine*. This early-stage project acceleration program gets high-level scientific and industrial experts involved in supporting selected projects until they reach the stage of maturity necessary for attracting investors or businesses. Six projects are currently supported by Springboard. The three projects selected in 2021 were 'Serointer-iron', headed up by Dr. Francine Côté and Prof. Olivier Hermine, to develop serotonin analogues to help with iron transit as new molecules of therapeutic interest; 'Pain in Children', led by Dr. Céline Gréco, to develop innovative treatment of pain management; and 'MSUD - Leukemia', led by Dr. Clément Pontoizeau and Prof. Manuel Schiff, to develop a gene therapy approach to leukemia.



Keratinocyte proliferation test (Alain Hovnanian Lab)

In 2021, the **Bioentrepreneurs program, created in 2016 to train young entrepreneurial scientists, engineers and managers in the biomedical field**, joined forces with the MedTech Generator & Accelerator initiative (SIA SATT-incubators-accelerators program of Investments for the Future (PIA), operated by BPI France). This consortium, led by *Institut du Cerveau (ICM)* in partnership with Institut *Imagine* and *Institut de la Vision*, aims to pool resources and provide researchers with innovative support programs that boost the development of start-ups specializing in health and AI in the fields of neuroscience and rare genetic diseases.

The **Innogrants program is focused on technology transfer**. Innogrants helps therapeutic or diagnostic innovation projects to get up and running and guides them in the early phases of development and proof of concept. Since its launch in 2018, it has already helped to get seven projects off the ground, one of which has led to the creation of a digital health start-up and two which are being incubated by the Springboard accelerator. In 2021, three new projects were selected following the call for proposals: a project headed up by Dr. Annarita Miccio and Dr. Edor Kabashi to develop genome editing tools for Amyotrophic Lateral Sclerosis (ALS or Lou Gehrig's disease) and proximal spinal muscular atrophy (SMA); another led by Dr. Mickaël Ménager and Dr. Frédéric Rieux-Laucat to identify and analyze a molecular profile for severe forms of Covid-19, especially pediatric myocarditis; and lastly, a project led by Dr. Céline Gréco, to research nanoparticles and pain management.

TWO START-UP SUCCESSES: MEDETIA AND CODOC

Medetia, the first start-up hosted on Institut *Imagine*'s Lab-in-Labs platform, is researching therapeutic molecules to treat rare pediatric diseases, particularly ciliopathies, which can seriously affect the kidneys and eyes. The founders of Medetia, Jean-Philippe Annereau and Luis Briseno-Roa, aim to develop therapeutic molecules to treat these diseases using a novel approach based on biological expertise, small molecules and artificial intelligence.

At Institut *Imagine*, the start-up is working with both the 'Molecular basis of hereditary kidney diseases' lab headed up by Dr. Sophie Saunier, who has identified half of the genes responsible for nephronophthisis and has co-developed along with Medetia a lead molecule for a future treatment, and the 'Ophthalmological genetics' lab led by Dr. Jean-Michel Rozet. Medetia also partners the *RHU C'IL-LICO* project, coordinated by Institut *Imagine*.

In February 2021, Medetia was selected in the *Challenges* list of '100 smart start-up investments in 2021'. In July 2021, Medetia was selected for the i-Lab innovation competition funded by the Investments for the Future

Program organized by the French Ministry of Higher Education, Research and Innovation in partnership with Bpifrance, with the aim of detecting innovative tech start-ups and supporting the best ones.

Codoc start-up was created in 2017 at Institut *Imagine* to offer hospitals installation, maintenance and training services enabling them to access and use 'Dr Warehouse', a data warehouse developed by the Institute's Data Science platform headed up by Nicolas Garcelon. Dr. Warehouse uses textual analysis to create cohorts for clinical trials, and to link apparently unrelated medical files to form groups of patients for research and gain a better understanding and diagnosis of certain rare genetic diseases. The warehouse currently contains de-identified data for more than 820,000 patients. In 2021, Codoc expanded its activity by deploying the warehouse at five new hospitals and developing new features. The start-up is managed by Arthur Delapalme, a graduate of the first intake of Institut *Imagine*'s Bioentrepreneurs program launched in 2016. This high-potential project was one of the first to be selected for the Institute's Innogrants program launched in 2017.

CARNOT: ADDING VALUE TO RESEARCH

Institut *Imagine* obtained the Carnot Institute label in 2020 enabling it to step up its research partnership activity. This is recognition of the quality of its relations with partners in the pharma sector and the socio-economic sphere involved in health innovation. In 2022, Institut *Imagine* will receive €1,020 million worth of funding for its research partnerships, 50% more than in 2021. This big increase is primarily the result of the government's wish to provide more incentives for public-private partnerships and increase the amount of Carnot funding under the French Law on research planning, as well as a significant increase in revenues from partnerships with

businesses and the socio-economic sphere, which form the funding base.

This funding helps to amplify research partnership activity and boost the impact of advances in diagnostic and therapeutic care by onboarding the businesses who will develop them and bring them to market.





REACHING OUT

'We expect researchers and scientists to explain their projects in a language we can understand so that we can help and support them. Patient organizations and the general public need to be more directly involved in research and be stakeholders in it.'

Gaëlle Marguin, Director of *Petit Coeur de Beurre*, an association of parents of children suffering from heart disease.

Speaking during the first dedicated patient association forum – *FAIR* (Forum of Associations of patients who *'Imagine'* what Research means) held on June 25, 2021.

One of Institut *Imagine*'s key missions is to transmit knowledge to scientists and physicians, students and young researchers as well as to the general public, patients and their families. The Institute strives to broaden research horizons as part of a relaxed two-way communication process in which we can explain what we know, what we do and what we have yet to discover, both inside and outside France. Sharing this engagement, enlarging our field of expertise and explaining and legitimizing our scientific approach based on hypotheses, experimentation and evaluation, allows us to provide patients with solutions as quickly as possible.

In 2021, the Institute worked towards this end by developing its program focusing on the Human and Social Sciences and its societal role, by revamping its programs to train the doctors and researchers of tomorrow, and by increasingly reaching out to the general public and patient organizations.

INSTITUT *IMAGINE*'S SOCIETAL ROLE: THE PROGRAM IS THREE YEARS OLD!

HUMANITIES, GENETICS, RESEARCH AND CARE @*IMAGINE*

Institut *Imagine* has one mission that is especially dear to its heart, namely, deploying a more humane vision of genetics and genomics to improve the quality of life of patients and their families in all areas, aside from just the treatment and scientific aspects. Genetic diseases are often associated with multiple disabilities and raise a whole host of questions concerning the place of those people affected in our society and the resources deployed to help both sufferers and their families live better quality lives with the disease.

The program to reach out to the Human and Social Sciences and promote the societal role of Institut *Imagine* was set up three years ago to improve the lives of patients, their families and loved ones, and to reflect upon the consequences of the disease.

It is headed up jointly by Laure Boquet, Executive Manager, Institut *Imagine*, and Dr Sandrine Marlin. The Steering Committee, comprising representatives of reference centers for rare diseases, patient organizations and the platform providing expertise in rare disease at the Necker Public Hospital for sick children, was expanded in 2021.



'This program is all about meeting and bringing together different people from different backgrounds – psychologists, sociologists, philosophers, linguists, designers, researchers and doctors – to understand what it is really like for families and help them to live better quality lives with the illness.'

Dr Sandrine Marlin

'At the juncture of multi-professional and multi-disciplinary expertise in the human and social sciences and rare diseases, Institut Imagine harnesses medical science and other resources to optimize the impact of this cross-fertilization, to improve the lives of families living with a genetic disease.'

Laure Boquet

REACHING OUT TO THE HUMAN AND SOCIAL SCIENCES AND PROMOTING THE INSTITUTE'S SOCIETAL ROLE MEANS:

1 OVERRIDING OBJECTIVE:

Improving the quality of life of patients and helping them to 'live with' the illness

4 KEY FOCUSES:

- Transmission and risk; wandering and uncertainty
- Educational integration, transition and socio-professional outreach
- Inclusion and quality of life
- Access to innovative therapeutic solutions

3 BASES FOR ACTION:

- Reaching out to non-medical research fields
- Development of pilot research and experimentation programs that may be spun off
- Reaching out to the general public, especially to young people

MULTIPLE PARTNERS AND PROJECTS:

Reference centers for rare diseases, patient organizations, Hospinnomics, EnsAD, EHESS, Institut de droit et santé, ENS, CERILAC, AgroParisTech (school specialized in life and environmental sciences), etc.



HUMAN AND SOCIAL SCIENCES AND PROMOTING THE INSTITUTE'S SOCIETAL ROLE IN 2021

05

MAY 2021

'IMAGINE LA SUITE', A SOCIO-PROFESSIONAL OUTREACH PROGRAM FOR PATIENTS

Headed up by Institut *Imagine* and Necker La Suite (Necker Hospital for sick children), and supported by Fondation Sycomore, this project aims to improve the lives of patients living with a genetic disease – from schooling to helping them transition into the world of work. As part of an internship program, a student at AgrosParisTech school – one of the partners in the project – drew up an inventory of the difficulties encountered by patients affected by genetic diseases. The program aims to build a personalized support system to help users gain access to higher education, professional training courses and jobs. Program continuity has been ensured thanks to the recruitment of a social worker specialized in supporting children affected by genetic diseases.

05

MAY 2021

HEALTH AND DESIGN: INVISIBLE DISABILITY

Since 2019, Institut *Imagine* and EnsAD (National higher institute for the decorative arts) have been deploying programs to experiment with new health-friendly design solutions as well as collaborative training and information-sharing initiatives. In May and June 2021, EnsAD, the Pratt Institute in New York and Institut *Imagine* launched a workshop on the theme of invisible disability. Students were able to talk to doctors, patient associations, psychologists and philosophers about disability, what it means, and the situations encountered by patients, their families and caregivers. They designed objects which were presented to a jury in June 2021. 'Tumi Stumi', a doll + app designed for children with anorectal malformations took first prize.

06

JUNE 2021

'REFLECTIONS' SENSORY WALL IMPACT STUDY

In 2020, an interactive digital work, created by the It is Now association and Dany Rose artists collective, was installed in the consulting area with the aim of reducing the stress involved in waiting, encouraging parent-child and child-child interaction, and allowing everyone to join in an unrestricted game. A study to assess the impact of the work was conducted in June 2021 by Chloé Dutruc, a student at EnsAD, as part of her internship on the theme of design and health. The study involved 96 families and doctors consulting *in situ* and it confirmed the positive impact of this wall on anxiety linked to waiting and the manner in which consultations proceeded. 75% of the health practitioners interviewed felt that the wall had a beneficial impact on consulting.





JUNE 2021

FAIR – FIRST DEDICATED PATIENT ASSOCIATION AND RESEARCH FORUM

In June 2021, Institut *Imagine* along with the platform providing expertise in rare diseases at the Necker Public Hospital for sick children, launched the first FAIR (Forum of Associations of patients 'Imagining' what Research means). Patient organizations were invited to discover the Institute's research labs through live virtual tours, interviews and a morning of exchanges with researchers, physicians and representatives of the reference centers for rare diseases.



JUNE 2021

REACHING OUT TO THE PUBLIC: LAUNCH OF SCHOLARSHIPS AS PART OF THE SCIENCE OUTREACH PROGRAM

Institut *Imagine*, with the support of Milk for Good and Fonds Derver, and in liaison with the BioSPC doctoral school of Université Paris Cité, has awarded three grants to PhD students tasked with showcasing the profession of researcher, raising awareness of genetic diseases and the role of research, and sharing the progress achieved by research into genetic diseases. They help to develop the Institute's policy of reaching out to the public through visits, workshops, meetings with schools and interns, deploying apps and 'science-made-easy' content, and raising awareness of programs dedicated to learning and the human and social sciences. The winners were Rachel Pereur, Anne Chalumeau and Miriam Villegas-Villarroel.



OCTOBER 2021

SECOND CALL FOR PROPOSALS IN THE HUMAN AND SOCIAL SCIENCES – RARE DISEASES

Institut *Imagine* has put out a call for projects to improve the quality of life of patients. The aim is to develop collaborative and cross-disciplinary projects in all fields of human and social science research applied to rare diseases treated in the Institute's affiliated reference centers. These projects must deliver a societal/patient/support impact that helps enhance care or quality of life. Three winning projects from the first call for tenders in 2021 have just been selected, focused around the themes of multiple disabilities and remote consultation, psychiatric patients with autism-type disorders, and the impact of announcement following screening for a rare metabolic disease.



FOCUS ON 'FAIR' FORUM OF PATIENTS ASSOCIATIONS 'IMAGINING' WHAT RESEARCH MEANS

3 OBJECTIVES:

- Sharing the progress of research and innovation in rare genetic diseases: being a standard bearer for research, making it more tangible *in situ* and exchanging over the research timeline.
- Closer integration of the associations affiliated to the reference centers for rare diseases, which are themselves affiliated with *Imagine* in both its *modus operandi* and in the team's research and care projects.
- Strengthening/forging interactions, especially during open lab sessions

2 HIGH POINTS IN 2021:

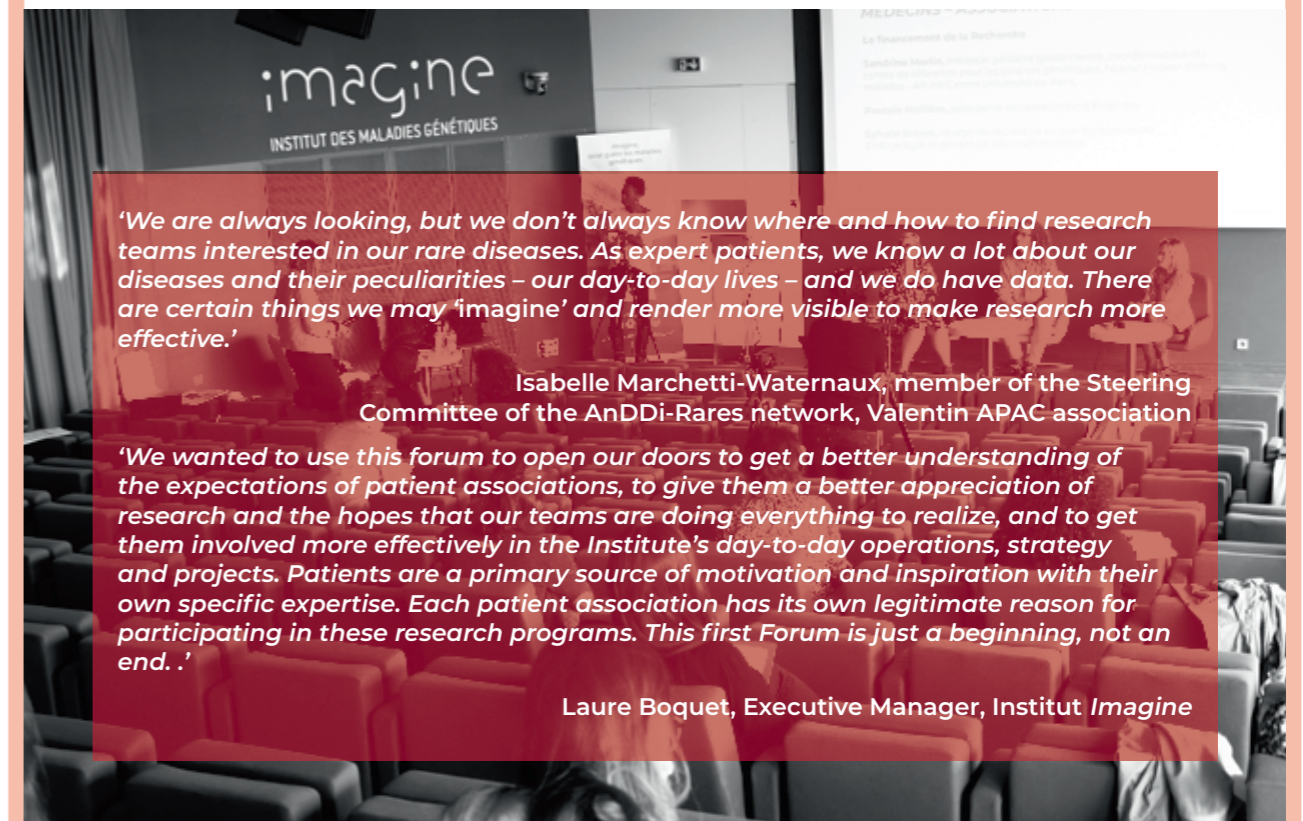
- 'Reporter for a day': virtual visits using a hand-held camera facilitated live exchanges

between scientists and patient associations in the labs.

- A morning of exchanges held via zoom featuring interviews and round table discussions was organized on June 25, 2021.

'FAIR' IN FIGURES

- **60** patient organizations involved
- **130** participants during the morning of exchanges
- **8** 'Reporter for a day' virtual visits in **10** research labs and **4** platforms
- **7** interviews to present the key actors in biomedical research.

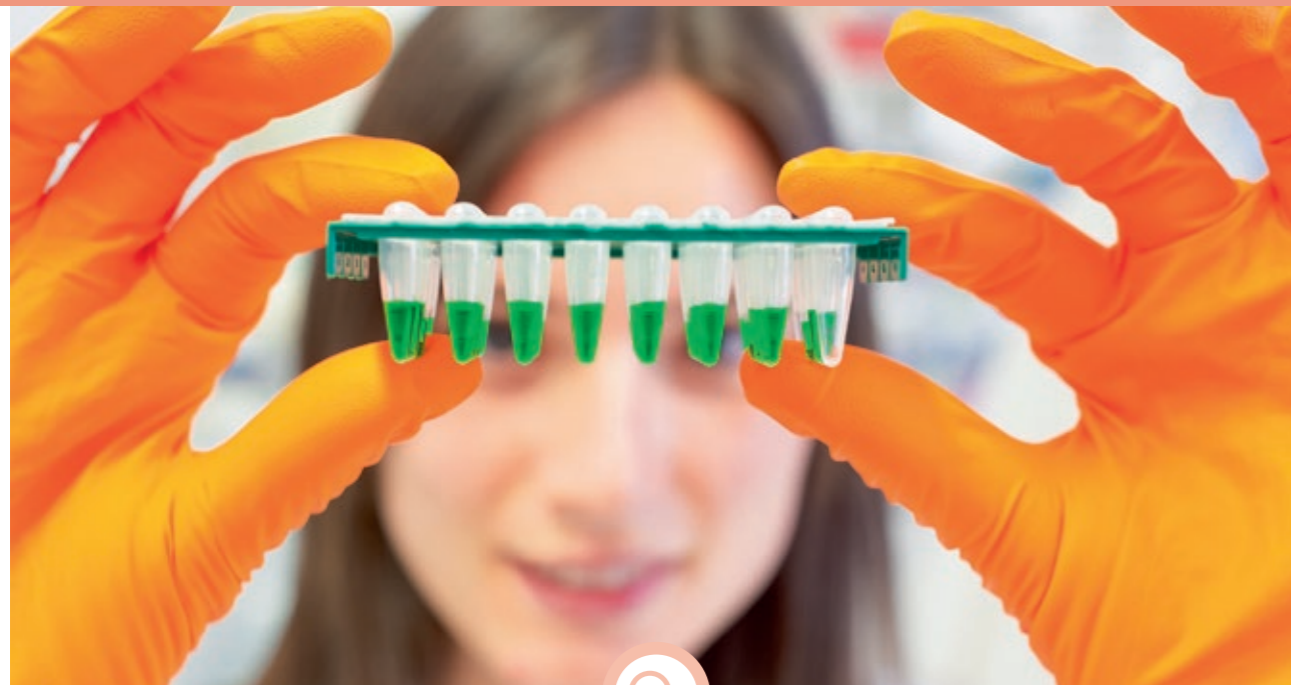


'We are always looking, but we don't always know where and how to find research teams interested in our rare diseases. As expert patients, we know a lot about our diseases and their peculiarities – our day-to-day lives – and we do have data. There are certain things we may 'imagine' and render more visible to make research more effective.'

Isabelle Marchetti-Waternaux, member of the Steering Committee of the AnDDi-Rares network, Valentin APAC association

'We wanted to use this forum to open our doors to get a better understanding of the expectations of patient associations, to give them a better appreciation of research and the hopes that our teams are doing everything to realize, and to get them involved more effectively in the Institute's day-to-day operations, strategy and projects. Patients are a primary source of motivation and inspiration with their own specific expertise. Each patient association has its own legitimate reason for participating in these research programs. This first Forum is just a beginning, not an end..'

Laure Boquet, Executive Manager, Institut *Imagine*



INTERVIEW: YOUNG RESEARCHERS FOCUSED ON SCIENTIFIC MEDIATION



Rachel Pereur, Anne Chalumeau and Miriam Villegas-Villarroel, who were awarded scholarships in the Science Outreach program launched in June 2021, exercised their talents as science mediators during the open days. Here, they talk about the reasons for their involvement.

Rachel Pereur: 'This program has one essential objective: making our work more accessible and more concrete. This is very rewarding, not just for the public but for us as well. The public gives us a different perspective and it is important to know how to look at things differently in order to move forward with our research.'

Anne Chalumeau: 'I am delighted to be able to share my passion for science with the wider public. This program allows me to grow and hone my skills. Making science more accessible is especially important to me because it allows me to showcase science and encourage new vocations in younger people.'

Miriam Villegas-Villarroel: 'This scholarship reconnects me with my passion for science. When you work day in, day out in the scientific domain, sometimes you can forget what attracted you in the first place. Communicating about what we do, especially to children and students who are wondering what path they will take, actually helps me to understand why I followed this path.'

'We are proud of this new team of scientific mediators, made up of an Education and Society program coordinator and young doctoral students eager to share what goes on behind the scenes in their fascinating profession, particularly with young people. This program has already demonstrated its social utility and impact, both for the general public and for the scholarship grantees.'

Laure Boquet,
Executive Manager, Institut Imagine.

TRAINING TOMORROWS' DOCTORS, RESEARCHERS AND BIOENTREPRENEURS

Institut *Imagine* offers under graduates, scientific and medical researchers and bio-entrepreneurs dedicated learning programs that promote dual research-medical skills. These programs are coordinated by Université Paris Cité – one of *Imagine's* founding members – together with its doctoral schools, and would not have been possible without the generous support of the Bettencourt Schueller Foundation, which has been an honorary benefactor of the Institute for the past ten years. At Institut *Imagine*, research-based and research-driven learning is illustrated by two strategic programs aimed both at attracting new talent and developing learning around new research and care imperatives.

A first review of research-based and research-driven learning

In early 2021, Institut *Imagine* and Fondation Bettencourt Schueller reviewed the first ten years of their work together. As one of *Imagine's* oldest patrons, the Foundation has been partnering its learning program, both by supporting the seminar center since 2011, which contributes to scientific outreach by organizing scientific conferences and debates, and by funding a chair. And since 2015, by supporting part of research-based and research-driven learning programs.

A FIVE-PART PROGRAM

MD-PhD: enables young doctors who already have a Master's degree in research to complete their training by doing a full-time scientific PhD at an Institut *Imagine* lab..

--> 27 candidates selected in 7 different sessions, including 16 funded by Fondation Bettencourt Schueller

'Temps protégés' (reserved time): aims to set aside time in which clinical specialists can conduct more clinical research projects.

--> 7 candidates selected and 2 extensions granted in 7 different sessions..

International PhD: allows international PhD students to complete their thesis at Institut *Imagine*.

--> 16 candidates selected in 7 different sessions, including 11 funded by Fondation Bettencourt Schueller..

4th year of thesis: enables PhD students to complete the experiments necessary for submitting articles and writing up their thesis.

--> 33 candidates selected in 6 different sessions, including 5 funded by Fondation Bettencourt Schueller.

Bioentrepreneurs Launchpad: a dynamic biotech enterprise program to accelerate high-impact healthtech start-ups. It is aimed at science, medicine, pharmacy, engineering and management under graduates.

--> 68 bioentrepreneurs trained in 5 intakes, including 29 partnered by Fondation Bettencourt Schueller which funded the first three student intakes.

KEY FIGURES

• €2,648,000 funded by Fondation Bettencourt Schueller

• 135 graduate alumni

• Including 68 who benefited from Fondation Bettencourt Schueller funding

Attracting international PhD students

In 2020, Institut *Imagine* teamed up with Institut Pasteur (Pasteur Paris-University – PPU) to create the PPU@*Imagine* call for proposals based on the International PhD program initially launched in 2014. The program is headed up by Dr. Frédéric Rieux-Laucat and consists of personal tutoring of PhD students and a range of workshops and related training. The extension of this call for proposals is a quality marker that has boosted attractiveness, driving a significant increase in applications from year one (298 versus 11) and more diverse candidate profiles (33 countries of origin versus 8). In 2021, three PhD students came to work in the Institute's labs and four more will begin their PhDs in October 2022 following the call for proposals put out in 2021.

IN 2021, THE PPU@IMAGINE CALL FOR PROPOSALS INCLUDED:

- **200** applications received
- **107** applications from doctoral students
- **10** thesis programs put forward by labs
- **31** different candidate nationalities
- **4** successful candidates



Supporting young researchers

31% of Institut *Imagine* members are either under graduates, PhD or post-doctoral graduates. Hiring and training the best talent means providing constant career-long support from the outset as well as a stimulating environment at the Institut itself.

SUPPORTING YOUNG CAREERS

Scholarships and funding have been created to help PhD students complete or continue scientific projects. Thus, PhD students may avail of a few months' worth of funding – known as 4th year of thesis – in order to complete and defend their thesis and 6 students received this type of funding in 2020-2021. The *Imagine* Thesis Award is also available to finance between three and twelve months of post-doctoral research for students who have published an article as author or co-author during the three years of their PhD. In 2021, two PhD students benefited from this funding.



YR2I – AN ASSOCIATION OF DYNAMIC YOUNG RESEARCHERS

Imagine's young researchers' association (YR2I) organizes scientific and social events throughout the year and supports young researchers by helping them to find their niche within the Institute and the wider scientific community. It also helps them to develop their skills and career perspectives. In 2021, young researchers were able to attend nine seminars where doctoral students practiced presenting their findings, five working breakfasts, training for doctoral competitions with a 100% success rate, invitations to international speakers, and the annual young researchers' congress, which brought together 110 participants remotely to give a series of pitches and scientific presentations.

A MEET-UP PLACE FOR POST-DOCTORAL RESEARCHERS

In 2021, '*Café des post-doctorants*' was organized on line on a regular basis by young researchers to facilitate meetings and exchanges, provide training on funding methods for post-doctoral research and advice on how to apply to research organizations. Young researchers may also take part in '*Café des chercheurs*' to discuss ongoing scientific activities at Institut *Imagine*, and '*Café des ITA*' (for engineers, technicians and administrators).

REACHING OUT TO THE WIDER PUBLIC AND YOUNGER PEOPLE

Two-way communication with the general public is essential for promoting and understanding *Imagine*'s activities, progress and projects and for raising awareness about genetic diseases, and the Institute has opened its doors and organized conferences for this very purpose.

A WEEKEND FOCUSED ON RARE DISEASES

Institut *Imagine* deployed all of its resources for International Rare Disease Day. On Saturday 27 and Sunday 28 February, in liaison with the Necker Public Hospital for sick children and its rare diseases platform, the Institute opened its doors virtually. Nearly 600 people participated in a dozen online conferences featuring trios of researchers, physicians, and patient associations discussing a variety of themes and diseases. All of these conferences are available on the *Imagine* website at www.institutimagine.org



ARCHITECTURE AND RESEARCH

On Saturday, September 18, *Imagine* opened its doors to the public, both physically and remotely on the occasion of European Heritage Days. The program of events included an exhibition, a virtual tour, lab visits, and a conference on 'Architecture in the service of research'.

CELEBRATING SCIENCE

More than 200 people attended the open day organized by *Imagine* on Saturday, October 9, 2021 to celebrate 30 years of *Fête de la Science*, featuring thematic conferences, tours, a career forum, an exhibition, and DNA extraction and cell microscope observation workshops for friends and families.



GETTING YOUNGER PEOPLE INTERESTED

In November and December 2021, 12 researchers from Institut *Imagine* took part in *Declics* (an initiative to promote dialog between researchers and high school students and get them interested in building knowledge) and they actually went out to meet the high school students for speed-dating sessions.

In addition, 23 of the many ninth grade interns hosted by *Imagine* in 2021 benefited from an outreach program set up at the end of the year, offering visits to the Institute and its platforms, microscope, DNA extraction and writing workshops as well as job speed-dating sessions.





COMMITMENT

'Institut Imagine represents a highly original model in the French healthcare landscape and we must continue to give this dynamic Institute all of the means necessary to ensure its continued success. Imagine is a place where generosity can have a multiplier effect on children's health and on family equilibrium.'

Anne and Henri de Castries,
Co-Presidents, Institut *Imagine* Major Donors Campaign

With the support of its Scientific Research Foundation, Institut *Imagine* draws on funding from both public and private sources, namely the French Government Investments for the Future (PIA) Program, founding members, industrial partners, Institut Carnot, and two exceptional initiatives: the *Heroes for Imagine* gala and the Major Donors Campaign. This synergy gives the Institute the independence and responsiveness it needs to remain at the leading edge of research into genetic diseases. At Institut *Imagine*, researchers and donors share values of excellence, high standards, a caring approach and respect, as part of a virtuous philanthropic circle underpinned by mutual commitment. There can be no real philanthropy without research and medical excellence, and no scientific achievements without generosity and private commitment. In 2021, when Institut *Imagine* launched its first Major Donors Campaign, our ambassador and donors were once again present at our side and greatly contributed to our collective struggle to change the lives of families affected by genetic diseases. Institut *Imagine* would like to express its heartfelt gratitude for their precious support.

'RESEARCH FOR EACH CHILD MEANS SOLUTIONS FOR ALL'

A MAJOR DONORS CAMPAIGN DESIGNED TO MEET THE CHALLENGES OF GENETIC RESEARCH

In December 2021, Institut *Imagine* launched its first public Major Donors Campaign, under the slogan 'Research for each child means solutions for all', headed up by Co-Presidents, Anne and Henri de Castries, and a committee of twelve ambassadors. The goal is to raise €40 million over five years and €12 million has already been raised, i.e. 30% of the target. The aim of this campaign is to harness the full potential of research into genetic diseases within Institut *Imagine* and accelerate its impact for the benefit of sick children and their families.

This campaign must make it possible to fund projects around three main focuses: deciphering DNA, sharing and training, and lastly, reflecting upon and developing the treatments of the future. Institut *Imagine* will use these initiatives to hire new scientific talent from among the best international teams, acquire the latest equipment, and deploy programs of excellence in its six priority areas of scientific and medical integration.

As Prof. Stanislas Lyonnet, Director of Institut *Imagine* explains, 'these projects will provide the best possible conditions for research to ensure that no child is left in limbo or without support, with ambitious objectives of doubling both the rate of diagnosis and the number of children with access to a clinical trial – from 15% to 30% of children diagnosed – by 2026.'



ANNE AND HENRI DE CASTRIES: COMMITTED CAMPAIGN CO-PRESIDENTS



'The future of millions of children and families affected by genetic diseases is currently in the balance at Institut Imagine. We are absolutely convinced that science and medicine are at a decisive historical crossroads and that the extraordinary technological transformations we are currently experiencing – combined with Imagine's best-in-class scientific and medical expertise – will help drive major advances in caring for sick children over the coming years. As this research has a direct impact on more common diseases, it also benefits medical knowledge more generally. Research performed for each child enables Institut Imagine to find solutions for all.'

Henri de Castries



'Incredible things are being achieved at Institut Imagine that provide immense hope for families. We have placed our trust in the teams because we have met with extraordinary men and women totally dedicated to the cause, who possess great humility and humanity. Working alongside Institut Imagine is also a way for us as parents to bring hope to entire families and siblings affected by illness.'

Anne de Castries

INSTITUT IMAGINE CAMPAIGN COMMITTEE



Patrick Aebischer



Gonzague de Blignières



Marie-Christine Coisne-Roquette



Dominique Gaillard



Sylvain and Michèle Hefès



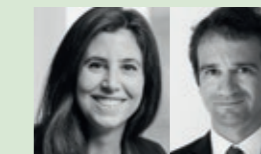
Sébastien de Lafond



Marie-Hélène and Jean-Bernard Lafonta

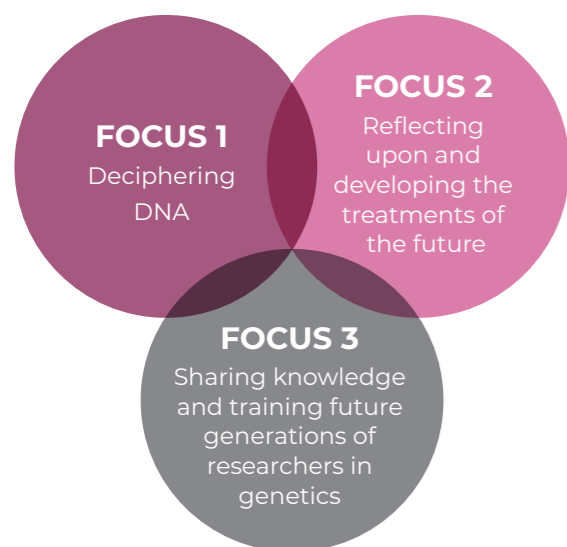


Frank Piedelièvre



Marie Schweitzer and Jacques-Antoine Philippe

THREE MAJOR FOCUSES



6 priority scientific domains

- ▶ Immunology
- ▶ Hematology
- ▶ Nephrology
- ▶ Neurological disorders
- ▶ Development abnormalities and cardiology
- ▶ Bioinformatics and data

MAJOR STRATEGIC PROJECTS

Examples of potential projects to be deployed thanks to the Major Donors Campaign

- ▶ **'HSS:** Human and Social Sciences, societal impact: designing and deploying a more humane form of genetics'
- ▶ **'Springboard:** accelerating innovation in genetic diseases and creating the biotechs of the future'
- ▶ **'Hematology:** providing innovative care to millions of children suffering from genetic blood diseases'
- ▶ **'Development and cardiology:** *Tête et Cœur* (Head and heart) Chair: providing innovative care to children with craniofacial and cardiac malformations
- ▶ **'Chair in developmental neurogenetics:** stepping up research into learning disabilities in children'
- ▶ **'International PhD:** inspiring and training the best international students in genetics'
- ▶ **'Cross-labs:** understanding and innovating together'
- ▶ **'Innogrants:** turning research into innovation'

'Institut Imagine offers us the possibility of building a future together for all of these children and coming up with the science of tomorrow'

THE CAMPAIGN IN FIGURES

- 5 years: 2021-2026
- €40 million
- €12 million already raised
- 1 presiding couple, 12 ambassadors
- x 2 the number of diagnoses
- x 2 the number of children with access to clinical trials

'Extraordinary causes call for extraordinary goals'

OUR UNSTINTINGLY LOYAL DONORS, PATRONS AND FRIENDS

In 2021, Institut *Imagine* was once again able to count on the commitment and enterprising spirit of businesses, foundations and donors in support of its missions.

'The commitment of donors – over and above financial support – is a real source of encouragement for all the Institute's research teams. Their support is proof that certain men and women are convinced that the future of research into genetic diseases is being played out today, right here at Imagine. Their commitment often goes way beyond financial generosity. Thanks to their vision, advice and networks, thanks to all the kindness, availability and confidence they afford the Institute, a wealth of new opportunities become available to deploy ambitious, innovative and impactful research for the benefit of sick children and their families. To paraphrase the Major Donors Campaign slogan: together along with our donors, we conduct research for each child that provides solutions for all. A big thank you to everyone!'

Laurent Mellier, Director of International Development and Philanthropy.

DIOR, COMMITMENT ON ALL FRONTS

In 2017, House of Dior and Institut *Imagine* created the 'Tailored medicine by Dior' Chair to come up with the medicine of the future via tailored medicine that combines the gene therapy expertise of Prof. Marina Cavazzana with the computational biology expertise available at Institut *Imagine*. This project, which has been extended through 2022, is generating very promising results in the field of gene therapy.



In the summer of 2021, Dior donated decorations initially created for Dior store windows in the fall of 2021. As part of an upcycling approach conducted with artist Marco Lodola, Dior brought art and beauty into the consultation areas of Institut *Imagine*-AP-HP (Paris public hospitals), inviting children and families to freely express their feelings through writing, drawing and coloring,

while bringing certain characters to life. Luminous and colorful figures installed in high places brought a comforting warmth to sick children and their families. 'Dior is using this interactive project to reiterate its support for medical research and patient well-being', explained Olivier Bialobos, Director of Communications, House of Dior, at the unveiling of the decorations.

Dior is very committed to children and care providers and wanted to bring a little seasonal joy to each in the form of a magnificent Christmas tree and gifts.

FONDATION BETTENCOURT SCHUELLER, ONE OF IMAGINE'S OLDEST PATRONS

The Bettencourt Schueller Foundation has been working alongside Institut *Imagine* since 2011, funding its seminar center and a chair in developmental biology. Between 2015 and 2020, it committed to financing research-based and research-driven learning programs (see overview on page 49). In 2021, the Foundation renewed this commitment by supporting a major new ambitious, high-impact area of research, namely the study of pain. The Foundation is therefore supporting the work led by Dr. Céline Gréco, to identify therapeutic targets in three of the most painful forms of chronic dermatological diseases. Céline Gréco leads the 'Pain in Children' group at the Necker Public Hospital for sick children and her research group has obtained the prestigious 'ATIP-Avenir' label.

COLAM INITIATIVES: INNOVATING AT THE INTERFACES TO SPEED UP GENETIC RESEARCH

To go further and faster in developing treatments for children suffering from genetic diseases, Institut *Imagine* has set up the Cross-Labs multi-team research program. Emerging projects bring research teams, technicians, reference centers for rare diseases and public and private partners together within a single working group. The contribution of a philanthropic partner is crucial in the start-up phase of such projects. It partners the project in its early experimental phase to reach proof of concept within three years. By supporting Cross-Labs in the early stages – considered by investors as the most risky – Colam creates the leverage needed to attract new national and international partners and financial backers, and encourages the development of larger-scale projects. A call for proposals was put out in November 2021. Colam Initiatives has committed to supporting this program over a five-year period and will be closely involved in evaluating, monitoring and rolling out the project.

AXA RESEARCH FUND: TACKLING CRANIOFACIAL AND CARDIAC MALFORMATIONS

In France, 3.2% of births are affected by congenital malformations, constituting a major public health challenge. The *Tête et Cœur* (Head and heart) research program, launched with the support of the Axa Research Fund, aims to identify the origins of these diseases and describe how they work in order to develop innovative and targeted treatments. It will also help develop cross-disciplinary talent and boost general awareness of the problems caused by congenital malformations. In 2021, thanks to the support of the Axa Research Fund, the program was launched and communicated to the public through articles and theses defended and presented at outside events and seminars, thus raising general awareness and interacting with patient associations. The five-year program will be rolled out with support from other benefactors.

ENTREPRENEURS FOR IMAGINE: UNDERSTANDING LEARNING DISABILITIES

Learning disabilities, or 'DYS' disorders (i.e., dyslexia, dysphasia, dyspraxia, dyscalculia, etc.) affect 6% to 8% of school-age children in France,

i.e. 1 to 2 students per class. 40% are afflicted by several DYS disorders: we refer to MultiDYS.

When tackling this health challenge, group force combined with entrepreneurial dynamism is an additional strength. At the initiative of Eric Perrier, President of Viseo, a group of six entrepreneurs and their families have teamed up to create 'Entrepreneurs for *Imagine*' to support the Institute's research into these disorders. The group has funded research to gain a better understanding of the genetic origins of MultiDYS in their extreme or family forms, to define these pathologies more effectively and identify clinical and even therapeutic diagnostic pointers for better patient care.

Fête de la Science provided an opportunity to celebrate, along with their families, their commitment to medical research for the benefit of disabled children, with a specially designed, fun educational tour of *Imagine*. During the day, the entrepreneurs presented *Imagine* with a €180,000 check for the amount of their first fundraising drive.



As Eric Perrier pointed out, 'Each entrepreneur's reasons for getting involved are always very personal, but there is no doubt that working together as part of a group is an incredibly rich experience. I am convinced that entrepreneurial daring should not only be deployed for business purposes but also for the common good.'

FONDATION SYCOMORE: SUPPORTING THE SOCIO-PROFESSIONAL INTEGRATION OF PATIENTS LIVING WITH A VISIBLE OR INVISIBLE DISABILITY

In 2021, Institut *Imagine*, with the support of Fondation Sycomore, launched '*Imagine La Suite*' to improve the lives of patients living with

a genetic disease – from schooling to helping them transition into the world of work (see page 45). This high-impact pilot project is rooted in the Institute's societal mission. Fondation Sycomore is committed to getting this four-year project off the ground and will be closely involved in subsequently tracking and deploying it. 'We were really touched by the tremendous commitment of the doctors and researchers who strive to reflect upon and deal with the social consequences of the disease to come up with solutions for integrating each patient into society. The project has captured the imagination of all our employees, two of whom have chosen to join the Steering Committee', explains Christine Tarbouriech, Executive Manager, Fondation Sycomore.

MILK FOR GOOD ENDOWMENT FUND AND DERVER FUND*: DEVELOPING SCIENTIFIC OUTREACH

In 2021, Institut *Imagine*, with the support of the Milk for Good Endowment Fund and the Derver Fund* (part of the Transatlantique Endowment Fund), launched a unique scientific outreach program in France whose quality and usefulness was validated by the Doctoral School. Part of Institut *Imagine*'s societal mission is to provide annual support to three students a year over a two-year period (see page 46 and interview on page 48). Deployment of this project to make knowledge accessible and transmit it between scientists and young people began in 2021. Thanks to these two patrons, three doctoral students were awarded a grant and have begun their public outreach activities with donor visits, workshops and tours organized during Institut *Imagine* open days.

HENNER AND ELSEVIER, STEADFAST SUPPORTERS OF INSTITUT IMAGINE



While certain businesses choose to provide support for one or more themes, others partner the Institute's priority projects by supporting its roadmap and general mission to battle genetic diseases. This is the case with Henner, a longstanding supporter of the Institute, and Elsevier. In 2021, Charles Robinet-Duffo, Chairman and CEO of Henner Group, presented a check for €10,000 to Institut *Imagine*. William Rubens, Director, France and Southern Europe, Elsevier Group, presented a check for €105,000.

A HEROES COMMITTEE AT THE READY

The fourth *Heroes for Imagine* gala will take place in 2022, an extraordinary auction of contemporary artwork and evening of exceptional events. Throughout 2021, the Committee met and worked hard on the organization of this evening, which has been headed up from the outset by Kamel Mennour, subsequently assisted by Didier and Clémence Krzentowski. It will be hosted by Gad Elmaleh and Christie's. The last time it was held in 2018, the event raised €7 million.

BOTH INDIVIDUALS AND PATIENT ASSOCIATIONS PLAY AN ESSENTIAL ROLE IN ACCELERATING RESEARCH

Throughout the year, families, patient associations and individuals all rallied around to contribute to the progress of research, showcase Institut *Imagine* and raise funds. To take a couple of examples, the KCNB1 association, chaired by Melissa Cassard, focuses on rare forms of epilepsy, and Noa Luu and her family battle the disease she suffers from, namely methylmalonic acidemia. The Lorre brothers launched a cycling challenge to draw public attention to this same rare genetic disease. And Patrice Brion, as a loyal donor, joined the selection jury for the call for projects for clinical research on rare genetic diseases launched by Institut *Imagine* and Necker Public Hospital for sick children. He told us that '*Being aware of what donations make possible is essential to being a donor. This has been a really rewarding experience. I gave my first vote to a project headed up by someone of exemplary scientific rigor but my second choice came straight from the heart.*'

TEDDY RINER, AN AMBASSADOR WHO HAS EMBRACED THE INSTITUT *IMAGINE* CAUSE

AN EXCEPTIONAL EVENT: TEDDY RINER AND LE BON MARCHÉ TEAM UP IN SUPPORT OF INSTITUT *IMAGINE*

Le Bon Marché department store and Teddy Riner teamed up over the Christmas period to boost awareness of Institut *Imagine* and raise funds for research. On December 9, 2021, a one-off auction was held along with Teddy Riner, hosted by Drouot auction house at Le Bon Marché department store, featuring Teddy's personal items including one of his kimonos and a black belt, as well as exceptional shared moments. The event also provided an opportunity for children to join in a photo shoot with Teddy. For the whole month of December 2021, teddy bears dressed in kimonos and the Institute's colors were sold in Le Bon Marché and the proceeds were donated to *Imagine*. Customers could also round up payments at the

cash register and make micro-donations to the Institute. The operation was a great success and raised €100,000.

'When Patrice Wagner, CEO of Le Bon Marché Group, asked us to partner with Institut Imagine, we were interested at once. Since its creation, Le Bon Marché has always been very engaged in social causes, particularly in support of health and children. Supporting a neighboring institute that is close to us and to our customers was really important to us. This project immediately resonated with all of our employees', according to Laurence Dekowski, Director of the Children's and Linen Department, and Olivier Di Maggio, Customer Relations Director. 'Teddy Riner is an extraordinary champion with a big heart. We were so lucky to be able to participate in this event with him.'



RAISING AWARENESS OF INSTITUT *IMAGINE* TO HELP MOVE RESEARCH FORWARD

Talking about genetic diseases and showcasing Institut *Imagine's* actions and the needs of research is also a means of contributing to the fight against genetic diseases. This is what our friends and supporters have achieved through various actions to raise awareness among the general public and health professionals.

ACIP SANTÉ'S POST-HOLIDAY CONFERENCE



On September 21, 2021, ACIP Santé organized its back-to-work conference at Institut *Imagine*, around the theme 'From Bench to Bed, *Imagine* as an innovation accelerator'. This event, organized in partnership with *Imagine*, boosted awareness of the Institute's model

among healthcare professionals and investors, and highlighted the specific features of research and the treatment of rare diseases and genetic disorders.

ESSEC BUSINESS SCHOOL: A MUSICAL COMEDY FOR RESEARCH

Students from the ESSEC Business School Musical association created, produced and performed a musical at La Cigale in September 2021. This highly successful initiative raised awareness of genetic diseases and research as well as raising funds. The students presented a check for €1,500 euros to Institut *Imagine*. 'They declared themselves delighted to be able to deploy such energy during Covid for the benefit of sick children.'

RADIO FRANCE: GETTING THE WORD OUT ABOUT BEQUESTS

In 2021, Institut *Imagine* laid the groundwork for a donation development strategy. To help raise awareness of the Institute and the possibility of making a donation to *Imagine*, Radio France offered to produce and broadcast two free radio spots. Thanks to this support, the voices of Sophie Saunier, a researcher in kidney disease at Institut *Imagine*, and Mélissa Cassard, President of KCNBI, who is closely involved with the Institute and mother of a small girl suffering from a genetic disease, were heard on the airwaves.

THEY'RE TALKING ABOUT *IMAGINE!*

871 articles in the media in 2021:

'Institut Imagine is only ten years old so we are a very young addition to the eco-system of research institutes and health and innovation stakeholders. We face a strong challenge to raise awareness of the Institute among the general public as well as among families in search of a diagnosis. In 2021, we initiated various actions to showcase Imagine and fulfill one of our

key missions: raising awareness of and providing information on genetic diseases. To become better known and more clearly identifiable, we have conducted digital campaigns, special operations, developed relations with the media, and organized conferences and open days for the general public. We have also been able to count on the unwavering support of our ambassador Teddy Riner to help us work towards this objective', explains Marie de Bazelaire, Communication Director at Institut Imagine.



A BIG THANK YOU TO ALL OUR DONORS!

Obviously, the major advances in genetics have been achieved thanks to doctors and researchers. But there are also thousands of other women and men who have helped to make such achievements possible:

You, our Donors.

At *Imagine*, we realize that it is by working together that we can make a real impact. Together, we can cure genetic diseases. Together, we will achieve progress that will benefit as many people as possible.

Everyone has a role to play and your role is decisive because everything starts with you. Your donations constitute the foundations of all our achievements and that is why we are more eager than ever to **share our successes with you.**

Thank you for your engagement, for the strength of your commitment and for your generosity.
Thank you for placing your trust in us.

And thank you on behalf of all the families and sick children you support.

PATRONS

Christian Dior Couture • Fondation Bettencourt Schueller • MSD Avenir • Anonymous.

MAJOR BENEFACTORS

Christie's • Fonds FAMA (part of the Swiss Philanthropy Foundation) • Galerie Kreo • Kamel Mennour • Hélène de Prittwitz • Michel and Fati Rosenberg.

BENEFACTORS

Azzedine Alaïa • Colam Initiatives • Fondation d'entreprise EDF • Axa Research Fund • Havas • HDL-JB Lafonta • Patrick Thomas.

MAJOR DONORS

Gonzague de Blighnières • Laurent Dassault • Gad Elmaleh • Elsevier BV • Entrepreneurs Amis d'*Imagine* • Fondation Colville • Dominique Gaillard • Jacques and Dominique Garaïalde • Groupe Galeries Lafayette • Sylvain et Michèle Héfès • Bernard Herbo • Philippe and Christiane Houzé • JC Decaux • Sébastien and Armelle de Lafond • Marcadé • Jacques-Antoine Philippe and Marie Schweitzer • François de Ricqlès • Anonymous.

DONORS' CIRCLE

Association KCNB1 France • Auxilium • Robert Bensoussan • Patrice Brion • Cyril Brulé • Alix and Edmond Cohen • Famille Cordier • Crédit Agricole d'Ile-de-France Mécénat • Fondation Sycomore • Fonds Derver (hosted by Fonds de Dotation Transatlantique) • Alix and Philippe de Fontenay • Groupe Etam • Groupe Henner • Groupe Lagardère • Bertrand and Marine Hainguerlot • Michel Jalon • Amin Khiari • La Boîte Immo • Le Bon Marché • Philippe Louis-Dreyfus • LVMH • Carine and Philippe Mareuil • Valérie Messika • Milk for Good • MK2 • Moët Hennessy • Monsieur and Madame Jérôme Péresse • Jacques Petit • Philippe Rousselet • Monsieur and Madame Sallé • Tollens • Bernard Valero • Josette and Jean-Claude Weill • Anonymous.



THE FAC ES BEHIND THE INS TITUTE

'Institut Imagine and the battle against genetic diseases are part of a collective approach. Imagine is first and foremost about women and men dedicated to and united around a cause, engaged and energized day-in, day out by their total commitment to sick children and their families.'

Laure Boquet,
Executive Manager, Institut *Imagine*



Institut *Imagine* brings together nearly a thousand research and care personnel dedicated to a single cause: changing the lives of families affected by a genetic disease. Researchers, doctors, engineers, technicians and students are assisted in their missions by *Imagine*'s support services and lab management teams.

24 RESEARCH TEAMS AND 4 ASSOCIATED LABS



► **L. Abel**
Human genetics of infectious diseases: complex predisposition



► **J.L. Casanova**
Human genetics of infectious diseases: monogenic predisposition



► **A. Hovnanian**
Genetic skin diseases: from pathophysiological mechanisms to treatment



► **S. Meilhac**
Heart morphogenesis



► **A. Pierani**
Genetics and development of the cerebral cortex



► **JM. Rozet**
Genetics in ophthalmology



► **J. Amiel**
► **S. Lyonnet**
Embryology and genetics of malformations



► **N. Cerf-Bensussan**
Intestinal immunity



► **E. Kabashi**
Translational research into neurological disorders



► **M. Ménager**
Inflammatory responses and transcriptome networks in diseases



► **A. Rausell**
Clinical bioinformatics lab



► **S. Saunier**
Hereditary kidney diseases lab



► **I. André**
Human lymphohaematopoiesis



► **Y. Crow**
Neurogenetics and neuroinflammation



► **A. Miccio**
Chromatin and gene regulation during development



► **S. Latour**
Lymphocyte activation and sensitivity to Epstein-Barr virus



► **G. Ménasché**
► **F. Sepulveda**
Molecular basis of altered immune homeostasis



► **F. Rieux-Laucat**
Immunogenetics of pediatric autoimmune diseases



► **V. Cantagrel**
Developmental brain disorders



► **O. Hermine**
Cellular and molecular mechanisms involved in hematological disorders and therapeutic implications



► **L. Legeai-Mallet**
► **V. Cormier-Daire**
Molecular and pathophysiological bases of osteochondrodysplasia



► **A. Rötig**
Genetics of mitochondrial diseases



► **JP. de Villartay**
► **P. Revy**
Genome dynamics in the immune system



ASSOCIATED RESEARCH LABS



► **N. Boddaert**
IMAGE@*Imagine*
3T MRI
Multimodal brain imaging



► **M. Polak**
Molecular endocrinology
Molecular bases of severe congenital and neonatal endocrine disorders and new therapeutic strategies



► **S. Sarnacki**
IMAG2
Computational anatomy for image-guided minimally invasive surgery in pediatric tumoral and developmental abnormalities



► **Y. Ville**
IMPACT@*Imagine*
Innovative and multidisciplinary prenatal approach to birth defects and their treatment

18 TECH PLATFORMS

PRE-CLINICAL



► **Emilie Panafieu & Pierre Chere**
Animal facility
Scientific ref.: Vincent Goffin



► **Nathalie Lefort**
IPS – Organoids
Scientific ref.: Leila Maouche-Chrétien



► **Sylvie Fabrega**
VVTG – Viral vectors and gene transfers
Scientific ref.: Sébastien Storck



► **Chiara Guerrera**
PPN – Necker Proteomics Platform
Scientific ref.: Alain Charbit



► **Pierre David**
Transgenesis
Scientific ref.: Jean-Pierre de Villartay



► **Marcelo Simon Sola**
AAV vectors



► **Meriem Garfa-Traoré**
Cell imaging
Scientific ref.: Gaël Ménasché



► **Sophie Berissi**
Histology
Scientific ref.: Fabiola Terzi



► **Corinne Cordier**
Cytometry
Scientific ref.: Emmanuelle Six



► **Ivan Nemazanyy**
Metabolomics
Scientific ref.: Mario Pende



► **Sorana Ciura**
Electrophysiology
Scientific ref.: Edor Kabashi

TRANSLATIONAL RESEARCH



► **Christine Bôle-Feysot**
Genomics
Scientific ref.: Annarita Miccio



► **Marie-Alexandra Alyanakian**
CRB
Scientific ref.: Corinne Antignac



► **Nathalie Boddaert**
3T MRI
Image@Imagine



► **Patrick Nitschké**
Bioinformatics
Scientific ref.: Jean-Philippe Jais



► **Nicolas Garcelon**
Data Science
Clinical databases and data warehouse



► **Mickaël Ménager**
Single-cell RNA transcriptomics



► **Stéphanie Moriceau**
Neuro behavior



THE EXECUTIVE COMMITTEE (G8) AND GENERAL SECRETARIAT

G8



► **Stanislas Lyonnet**
Director
Embryology and genetics of malformations



► **Laurent Abel**
Human genetics of infectious diseases: complex predisposition



► **Olivier Hermine**
Cellular and molecular mechanisms involved in hematological disorders and therapeutic implications



► **Frédéric Rieux-Laucat**
Immunogenetics of pediatric autoimmune diseases



► **Nathalie Boddaert**
Image@Imagine
3T MRI



► **Anita Burgun**
Medical Informatics



► **Alessandra Pierani**
Genetics and development of the cerebral cortex



► **Sophie Saunier**
Hereditary kidney diseases

GENERAL SECRETARIAT



► **Laure Boquet**
Executive Manager



► **Laurent Mellier**
International Development and Philanthropy



► **Hélène Chautard**
Innovation and Technology Transfer

DEDICATED WORKING GROUPS (WPS)



WP 1: Developing exceptional cohorts
► Rémi Salomon & Nicolas Garcelon



WP 2: Developing genomic and bioinformatics platforms
► Corinne Antignac



WP 3: Promoting pathophysiological research
► Isabelle André & Agnès Rötig



WP 4: Developing innovative therapies
► Olivier Hermine



WP 5: Recruiting new talent
► Stanislas Lyonnet & Jean-Laurent Casanova



WP 6: Developing learning and training programs
► Frédéric Rieux-Laucat



WP 7: The human and social sciences and societal role of the Institute
► Laure Boquet & Sandrine Marlin

WP 8: Management and development

WP 9: Industrial and institutional projects

WP 10: Real estate and operations

SUPPORT SERVICES



► **Nathalie Wuylens**
Legal Affairs



► **Hélène Chautard**
Innovation and Technology Transfer



► **Recruitment pending**
Clinical research



► **Laurent Mellier**
International Development and Philanthropy



► **Marie de Bazelaire**
Communication



► **Séverine Delalande**
Programming and Finance



► **Sara Lenoir**
Human Resources



► **Marie-Pierre Sarrazin**
Administrative coordinator of mixed research unit (UMR)



► **Anne-Marie Laurencine**
Health, Safety and the Environment



► **Cécile Bureau**
Internal Services



► **Jérôme Flatot**
IT Services



► **Stéphane Paillet**
Operations



HUMAN RESOURCES AND DAY-TO-DAY LIFE AT THE INSTITUTE

Institut *Imagine* provides its employees with a rich and varied worklife through events that encourage exchanges, synergies and internal cohesion, and by supporting associations that organize professional, scientific, social and sporting activities.

DYNAMIC CLUBS AND ASSOCIATIONS

Against the backdrop of the pandemic, YR2I (*Imagine's* young researchers' association) and ISA (the *Imagine* sports association) have doubled down on inventive initiatives. The Young Researchers' Congress brought together 110 participants remotely to present their research projects and organize rival pitches and image competitions. As Romane Thouenon, then President of YR2I commented, 'we are delighted to have been able to organize this congress in these very unusual circumstances where young researchers and students are in even more need of support and exchanges.' The sports association kept up its courses remotely and then face to face, as well as outdoor or virtual sports events such as rock climbing, tree climbing and running. The two associations also organized a hybrid Olympics, a fun and creative event between different Institut *Imagine* teams.

SCIENTIFIC AND MEDICAL EMULATION

Institut *Imagine* organized regular 'Monday Seminars' throughout 2021 given over to scientific and medical exchanges. They allow researchers from

Imagine's labs and from the campus, as well as guest researchers from France and elsewhere, to keep abreast of and learn from each other's research progress. Seminars for young researchers are also organized by YR2I to prepare PhD students to defend their thesis. iCARPs meetings (i.e., Integrated Care And Research Programs) are held on a regular basis to discuss the Institute's priority research and care focuses.

ONBOARDING EVENTS

A number of initiatives were organized in 2021 to inform and rally personnel, provide a convivial setting, and promote the spirit of the Institute. LIVE (Link Information Visual Exchange) events were inaugurated in November 2021 aimed at sharing and exchanging information internally about *Imagine's* short- and medium-term challenges, including the Institute's scientific brief, governance and scientific and institutional projects. The European soccer championships held in June-July 2021 provided an opportunity to rally teams around a major prognosis challenge. In October 2021, *Imagine* celebrated science in-house with a big interactive game and a scientific image contest that culminated in an exhibition. Moreover, the 'Café des chercheurs' and similar get-togethers for post-doctoral students, engineers, technicians and administrators also provide a forum for interaction and exchanges.



A QUALITY WORK ENVIRONMENT AND SUSTAINABLE DEVELOPMENT: TWO KEY FOCUSES

Since its foundation, Institut *Imagine* has placed corporate social responsibility and sustainable development at the heart of its *modus operandi*. Every year, the Institute evaluates the quality of its work environment, working conditions, the environment of its employees, as well as feelings and demands relating to teleworking, in order to identify areas requiring specific action. As part of Quality of Life at Work Week in June, two workshops were organized: one on returning to the office and getting back to everyday life after the pandemic, and another to promote the benefits of 'catnaps'.

Other actions have been deployed to reduce Institut *Imagine's* environmental footprint. In 2021, bean-to-cup coffee machines donated by JURA and coffee distributor Action Café were installed to reduce the

use of capsules, cut down on waste and encourage more responsible consumption.

During European Sustainable Development Week, there was a focus on the waste sorting system introduced in 2020 with collective sorting bins and the issue of digital waste, and employees were able to attend a conference on waste reduction solutions.

GENDER EQUALITY: A MAJOR PRIORITY FOR IMAGINE

Imagine achieved a satisfactory gender equality score of 84 out of 100 based on the four official indicators, similar to that of 2020. In 2021, the Institute continued its commitment and initiatives to ensure gender equality and promote professional diversity and mix. A specific program was launched at the end of 2021 and two gender and professional equality advisors were appointed to assist management in deploying these actions.

SOCIAL PERFORMANCE REPORT

UMR (mixed research unit)
no. 1163

The figures provided in this social performance report cover all personnel working in the *Imagine* building.



WORKFORCE

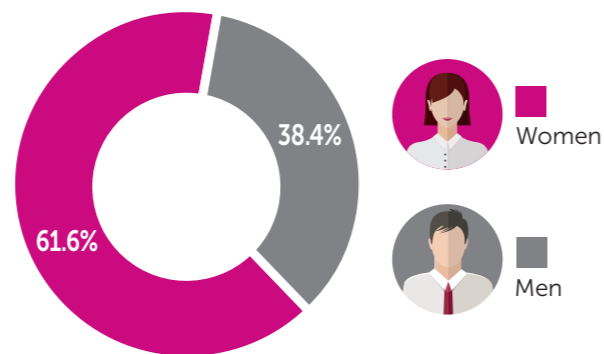
At 12/31/2021

591 EMPLOYEES

512.23 FULL-TIME EQUIVALENTS (FTE)

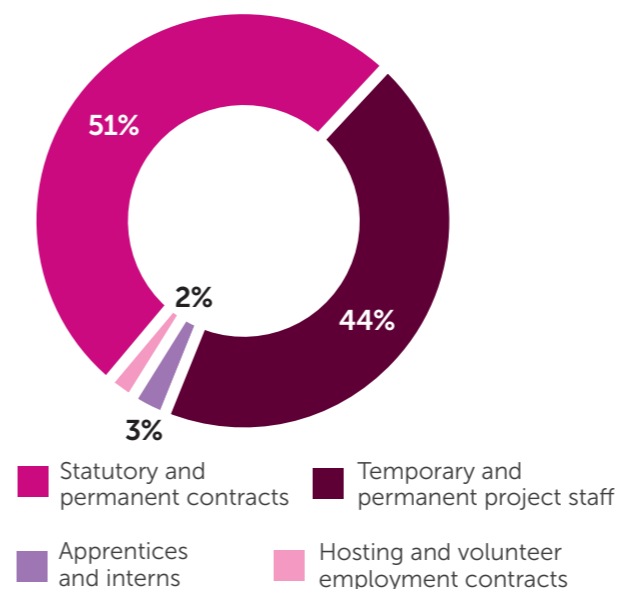
We note an increase of 8.63% (591 employees at 12/31/2021 vs. 544 at 12/31/2020). The proportion of women and of men remained stable year on year.

Breakdown of employees by gender at 12/31/2021

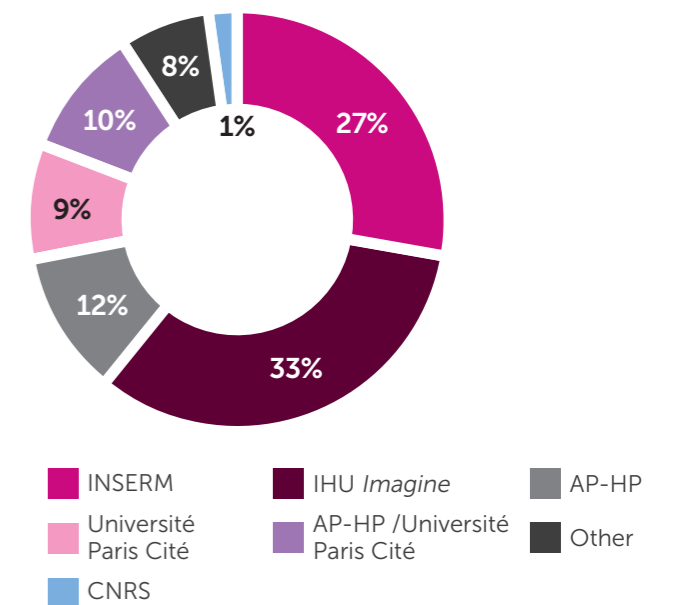


EMPLOYMENT

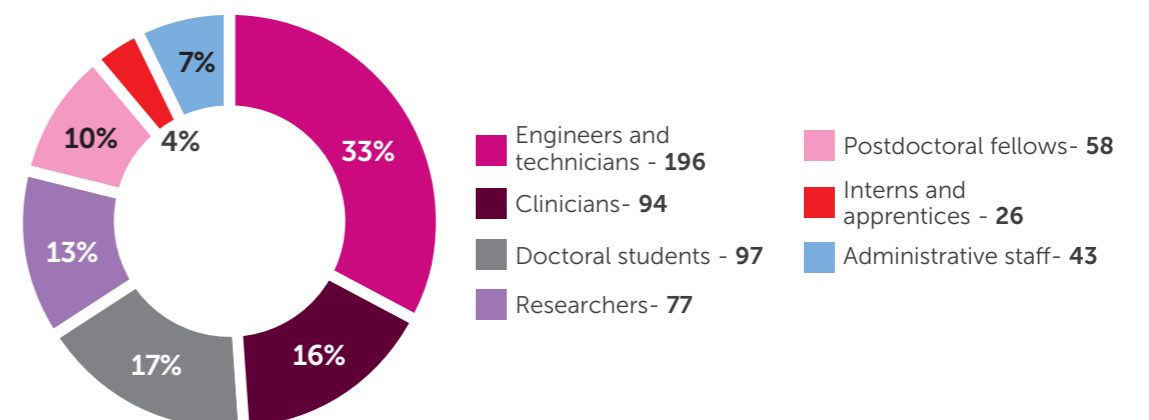
Breakdown of employees by type of employment contract at 12/31/2021



Breakdown of employees by employer at 12/31/2021



Breakdown of employees by type of employment at 12/31/2021



AFRICA

SOUTH AFRICA: **1** - ALGERIA: **12**
MOROCCO: **4** - SENEGAL: **1** - TOGO: **1** - TUNISIA: **2**

AMERICA

ARGENTINA: **1** - BOLIVIA: **1** - BRAZIL: **5** - CANADA: **3**
CHILE: **2** - COLOMBIA: **2** - CUBA: **1** - MEXICO: **3**
VENEZUELA: **1**

ASIA

CHINA: **3** - SOUTH KOREA: **1** - INDIA: **5** - IRAN: **3**
JAPAN: **2** - LEBANON: **5** - PHILIPPINES: **1** - THAILAND: **1**

EUROPE

GERMANY: **6** - UK: **2** - AUSTRIA: **1**
BELGIUM: **3** - BULGARIA: **2** - DENMARK: **1**
SPAIN: **10** - FRANCE: **469** - GREECE: **3**
ITALY: **23** - LITHUANIA: **1** - LUXEMBOURG: **1**
POLAND: **1** - PORTUGAL: **4** - ROMANIA: **2**

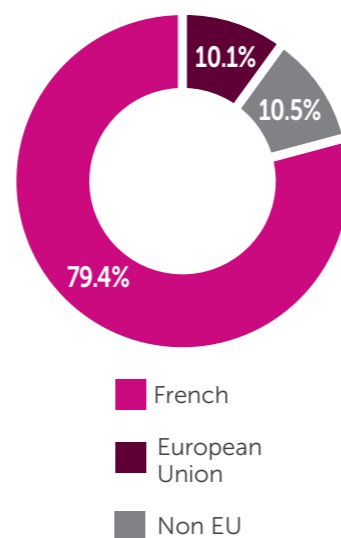
OCEANIA

AUSTRALIA: **1**

The proportion of international employees has increased slightly to over 80%.

37

NATIONALITIES

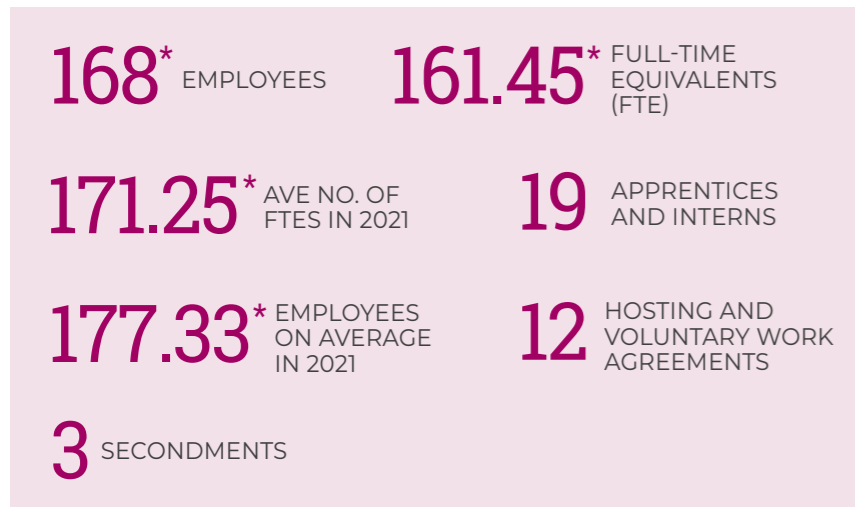


Fondation Imagine

These figures only include staff actually employed by Imagine Scientific Research Foundation.

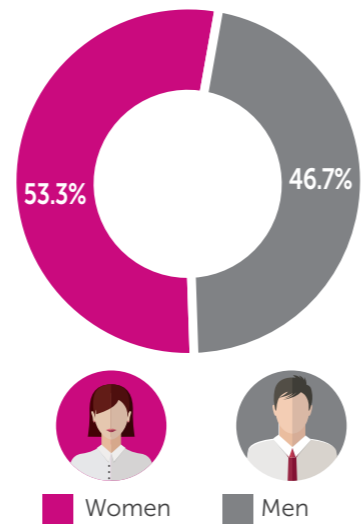
WORKFORCE

Workforce at 12/31/2021

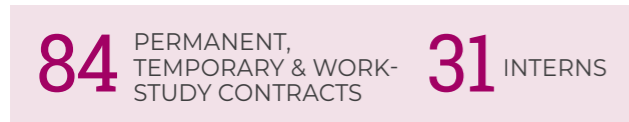


* Excluding apprentices and interns

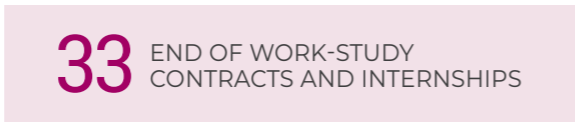
Breakdown of employees by gender at 12/31/2021



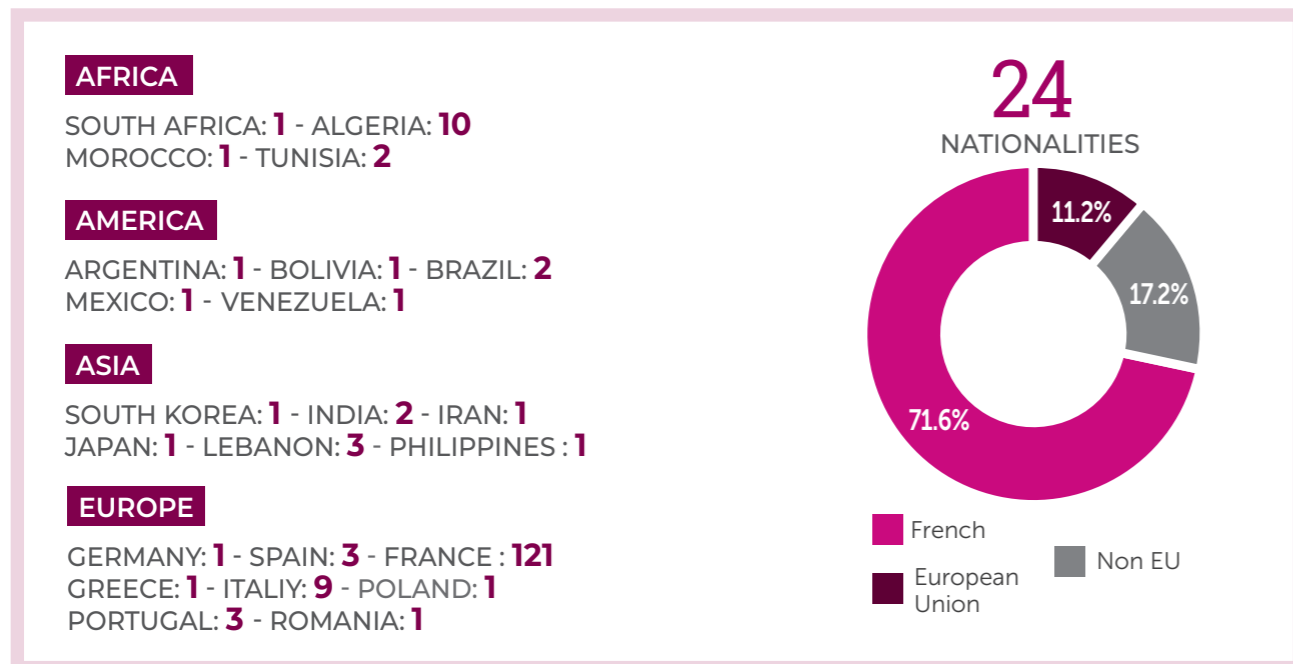
115 new contracts in 2021 o/w:



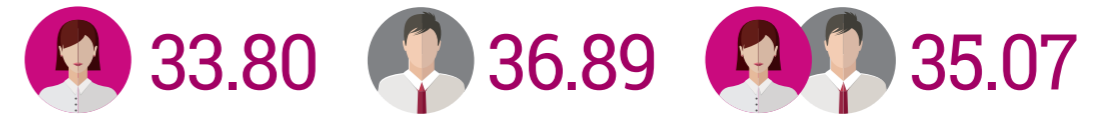
102 contracts completed in 2021 o/w:



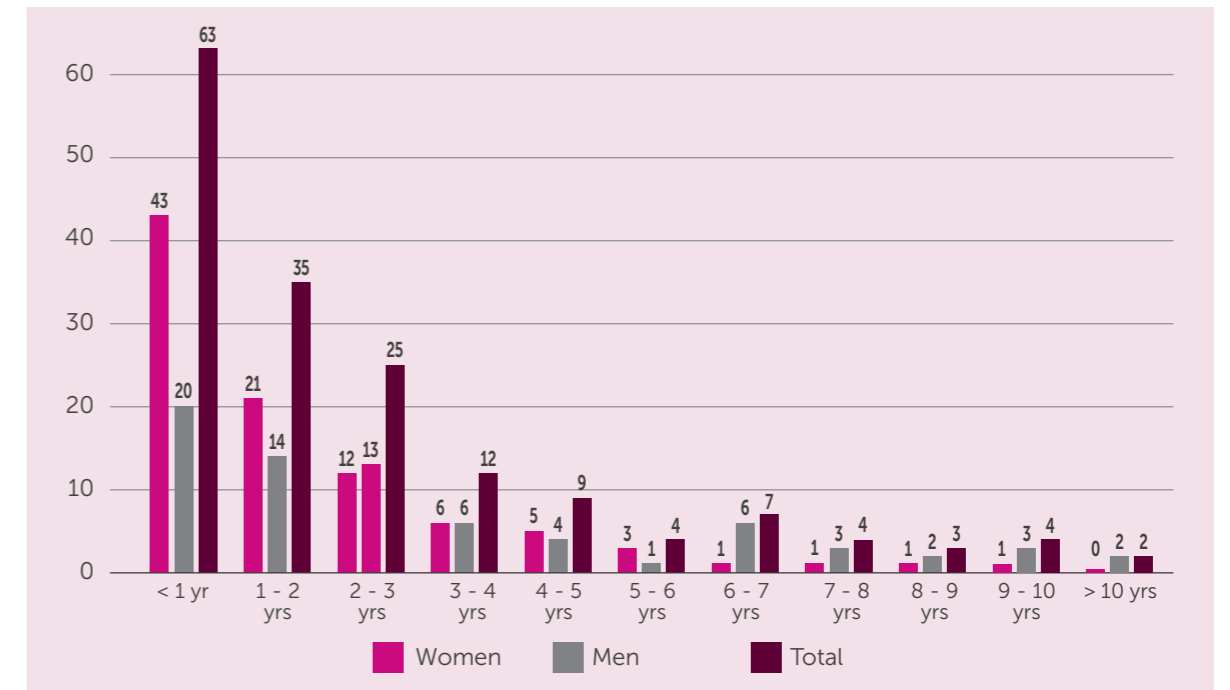
Employee nationalities at 12/31/2021



Average age of employees at 12/31/2021 *



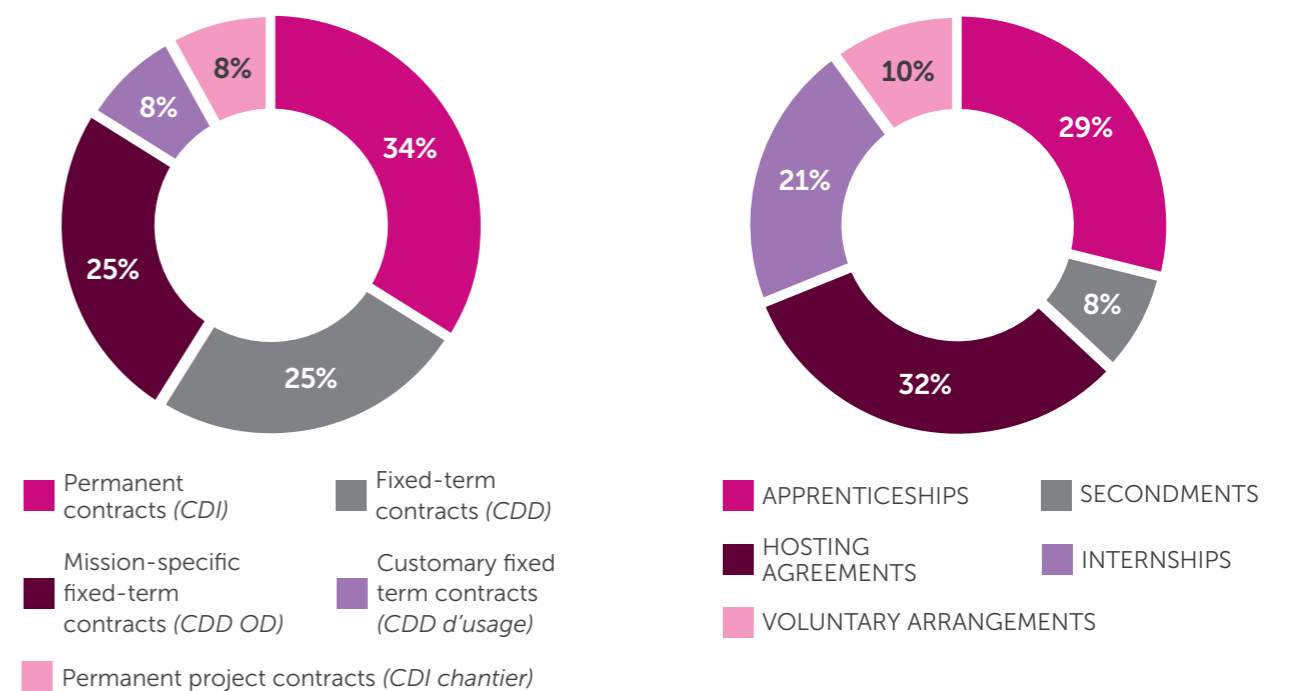
Employee length of service at 12/31/2021 *



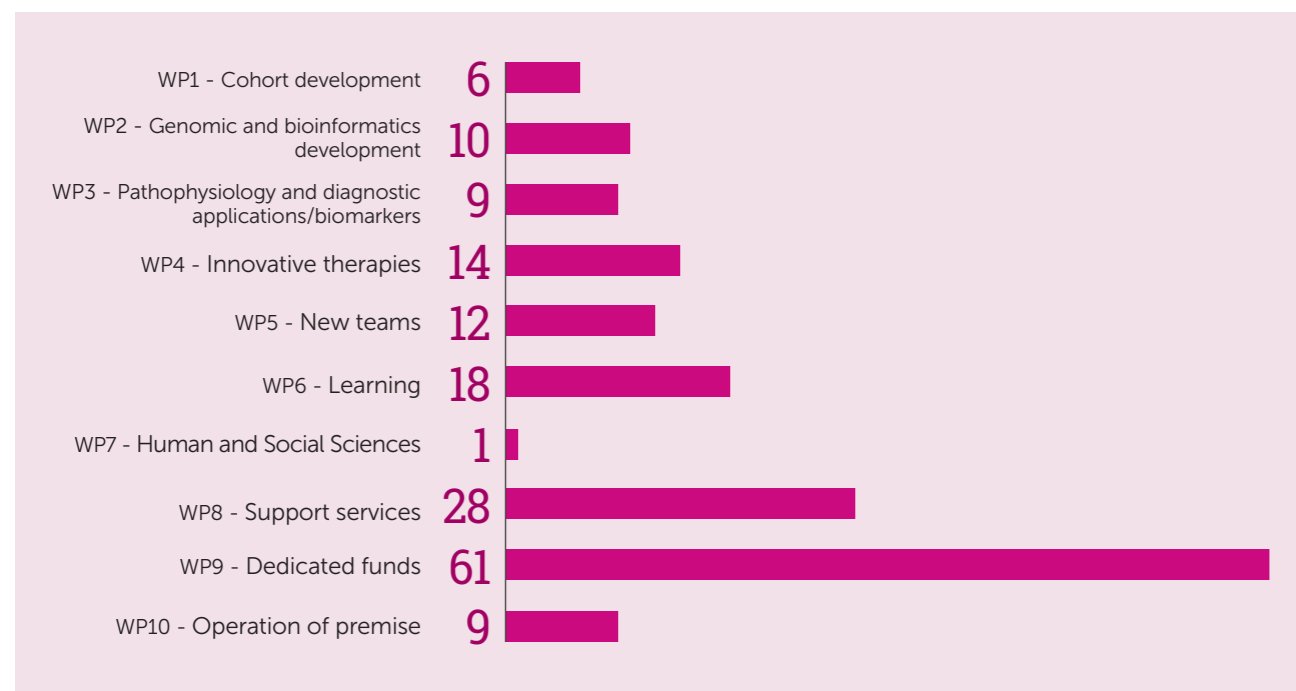
* Excluding apprentices, interns, employees on secondment, and hosting and volunteer employment contracts.

EMPLOYMENT

Breakdown of employees by type of contract at 12/31/2021



Breakdown of employees by work-package (IHU program) at 12/31/2021

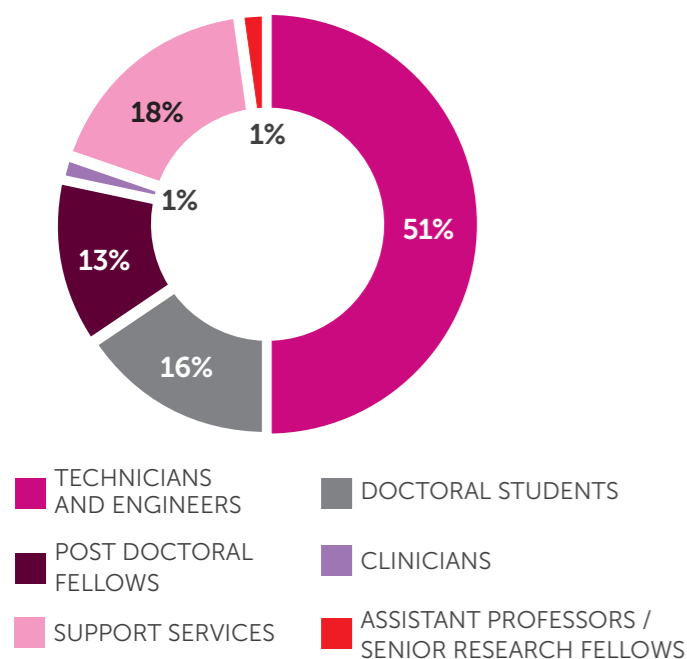


Gender equality indicator *

84/100

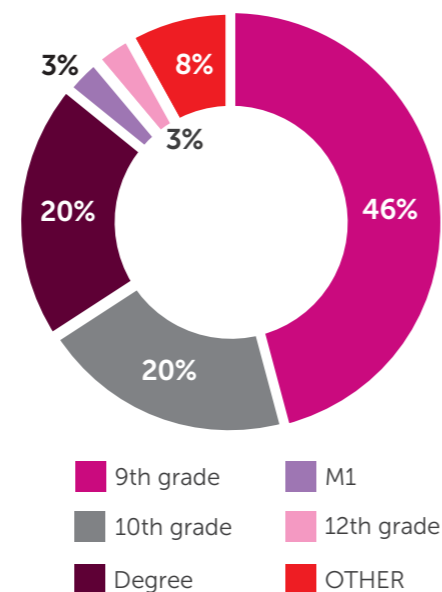
* Based on 4 indicators: pay differentials, pay increase differentials, % employees who received a pay increase in the year following their return from maternity leave, number of employees of the under-represented sex (men) among the 10 highest salaries.

Breakdown of employees by occupational category at 12/31/2021



INTERNS

Number of internships in 2021 lasting less than one month: **39** (417.5 days)



OUR FINANCES

2021 FINANCIAL YEAR

THIS WAS *IMAGINE'S* THIRTEENTH FINANCIAL YEAR

2021 was a year of transition, dominated by the continuing impact of the health and economic crisis since the spring of 2020. Deployment of all of the programs and measures set out in *Imagine's* roadmap was generally behind initial objectives, however this was offset by the resumption of sustained research momentum thanks to significant mobilization of private funds in addition to donations and philanthropy, and successful bids for major projects, reflected in the progress made by the teams in driving their research projects forward.

In 2019, which was a pivotal year, Fondation *Imagine's* accreditation as a University Medical Institute (*IHU*) was extended by decision of the Prime Minister through 2020-2024, and *Imagine* also received additional funding of €17 million under the French Government Investments for the Future (*PIA*) Program. 2020 was dominated by the health and economic crisis, resulting in more stringent oversight of the programs set out in the Institute's roadmap (i.e., conditional implementation, rounding or postponement) and responses that involved rethinking funding models and maintaining project development at a high level despite the difficult circumstances.

2021 required a similar balancing act with a focus on continuing to deploy the strategic priorities set out in the **new 2019-2028 roadmap**, while returning to strong growth in external, public and private funding, reflecting the degree of maturity achieved by the Institute and its ability to withstand the current crisis.

The **unprecedented health and economic crisis** of 2020 and 2021 has checked the Foundation's momentum, requiring it to adopt a very prudent approach, which was debated and validated by its Governing Board at the different meetings held in 2020 and 2021.

The provisional budget for 2021 was approved on the basis of a projected deficit and a number of pessimistic assumptions which, when corrected would boost income, and said deficit was offset in full by reserves set aside in previous years.

Balancing the books in this manner was presented as involving a significant risk in terms of income from collective fundraising.

This risk was estimated and forecast by pre-identifying a range of contingency measures, which if postponed, would enable savings to be made.

The management approach was underpinned by a methodology built around three dimensions (the core program, acceleration program, and execution of contracts hosted out of acquired income), a finely-tuned approach to allocating income to each item of expenditure and monthly sequencing of all measures. Management of the risk incorporated into the model was based on retained earnings, potential acceleration of consumption of PIA-IHU funding and, as a last resort, 'as an exceptional measure after all of the Foundation's other resources have been exhausted', recovering part of the initial endowment. The **Governing Board approved this strategy** based on the idea of harnessing all of the solidarity and goodwill generated by the results of the Institute's research teams focused on COVID 19, among *Imagine's* founders, who have renewed their support, and its donors, whose loyalty has been apparent from the onset of the crisis (Heroes community and Major Donors Circle).

In May 2021, the Board exhorted the Institute to step up its momentum while maintaining a tight rein and a prudent management approach.

The **2021 financial year closed with a net surplus** despite the onerous impact of the crisis. This better-than-expected result reflects the Institute's prudent management based on a level of risk in line with assumptions concerning collective fund-raising.

The surplus, which exceeded forecasts, is mainly attributable to:

- accelerated consumption of PIA-IHU funding, as decided by the Board in May 2021 (+€0.9 million),
- substantial savings generated by execution of contingency measures (+€1 million),
- non-occurrence of pessimistic assumptions included in the budget (COVID contingencies, contract contingencies, etc.) it +€0.6 million,
- postponed implementation of (non-contingent) acceleration measures (+€1.4 million),
- miscellaneous savings in payroll, services and project costs attributable to a slowdown in certain programs (+€1 million, including over €0.4 million for the Heroes event).

Moreover, the negative impacts of the health and economic crisis are attributable both to the **suspension of large sums obtained from public generosity** and the necessary postponement of certain measures:

- postponement of the Heroes charity gala for another year,
- postponement of the search for major international donors,
- postponement of expenditure on **industrial and clinical research contracts**,
- decisions to **postpone a certain number of actions and related expenditure until 2022**,
- **automatic postponement of recruitments and a slowdown in the deployment of projects**, especially those based on *Imagine* calls for tender.

However, these negative impacts were offset by a **sustained dynamic** reflected in:

- the **increased generosity of major donors** who rallied around the campaign President, and the **marked commitment of new associations, foundations and endowment funds**,
- a **major increase in public subsidies**, despite the significant amounts of reserves of deferred income and dedicated funds set aside at the end of the year, which will have a positive impact on growth in 2022,
- the continued **development of platforms**, particularly in data science and single-cell analysis. Moreover, acquisitions, recruitments and work on the **neurobehavioral platform** were carried out in support of the priority focuses of the Institute's scientific strategy.

All of these movements culminated in a **10% increase in income**, giving an **overall surplus of €2,549 million**, which must be corrected for accounting adjustments totaling €1.5 million.

A measured approach was adopted over the financial year so as not to jeopardize the implementation of the IHU roadmap, especially its strategic priorities – validated by both the International Scientific Advisory Board and the Governing Board. Priority was given to scientific resourcing, requiring in particular the maintenance of the IHU core program, launch of the 'new team' international call for tenders in the field of neurodevelopment, and continuation of the Crosslab and Springboard programs (financial and expertise accelerator), contingent on additional Go/No Go phases that make it possible to manage risk. The postponement of these *Imagine* calls for tenders to the second-half of 2021 automatically deferred the related expenditure from 2021 to 2022.

This management approach was deployed in a context of **financial strength**, as reflected in the Institute's **own funds** (the initial endowment of €12.9 million has been reconstituted in full by surpluses generated in previous years; retained earnings

amounted to €3.1 million at end-2020) and its **cash balance** (€20.2 million as of December 31, 2021, excluding capital invested in an endowment contract for an amount of €3.7 million). This financial strength will be bolstered by the significant surplus generated in 2021. It is also reinforced by extension of the IHU label through 2024, and very possibly beyond this date as the government announced in March 2022 its intention of continuing to support the University-Medical Institute (*IHU*) business model by potentially awarding an additional grant for 2025-2030, subject to vetting by an international jury.

2021 reflects the **multi-annual development of the Institute's activities** in view of the growth in the major cross-cutting programs: following the DIM gene therapy contract secured in 2016 (€9.5 million over four years, extended for a fifth year with additional funding announced at the end of 2020 and confirmed in early 2021), the RHU3 C'IL-LICO project secured in 2017 (*ANR-PIA* funding of €5.9 million over five years), the RHU4 primary immunodeficiency project secured in 2019 (*ANR-PIA* funding of €9.9 million over five years), in December 2021 the Institute was awarded coordination of a third *RHU* program in the fifth wave of calls for *RHU* projects, dedicated to the development of treatment for COVID-19 (€10 million over five years).

Obtaining the **INSTITUT CARNOT** label, which recognizes the value of the dynamic partnership with the socio-economic sphere, culminated in fresh public funding for 2021, which has been partially consumed due to the postponement of projects financed by Innogrant.

Finally, the generosity of *Imagine's* **major donors** is reflected in sizable multi-annual commitments and 2021 was marked by the end of the 'silent phase' of the campaign presided over by Anne and Henri de Castries. In late 2021, they officially announced their aim of raising €40 million between 2020 and 2028, while more than €12 million has already been promised over several years by the circle of major donors.

The notes to the 2021 financial statements provide details of the annual financial statements of Institut *Imagine* for the year ended December 31, 2021. The 2021 accounts are presented in accordance with the new accounting regulation No. 2018-06.

The financial statements for the year ended December 31, 2021 show total assets before appropriation of **€82,836,897** (compared to total assets of **€84,278,228** at end-2020).

The income statement presents a surplus of **€2,549,470** (compared with a surplus of **€3,016,000** for 2020).

An analysis of the 2021 financial statements highlights the following figures:

1. Balance sheet

The balance sheet provides a summary of the financial position of *Imagine* in terms of sources and uses at the accounts closing date, i.e., December 31, 2021.

Total assets amounted to **€82,836,897** at this date, compared to **€84,278,228** at December 31, 2020. This lower amount is attributable to a decrease in deferred income, especially in relation to *PIA-IHU* funding.

Net assets	12/31/2021	12/31/2020	%
Fixed assets	€9,488,220	€10,449,697	-9%
Current assets	€73,348,677	€73,828,531	-1%
Total	€82,836,897	€84,278,228	-2%

Net funds and liabilities	Net funds and liabilities	12/31/2021	%
Own funds	€22,010,780	€20,145,281	9%
Loss and contingency provisions	€995,453	€1,047,196	-5%
Dedicated funds	€2,948,570	€2,368,660	24%
Liabilities	€56,882,094	€60,717,091	-6%
Total	€82,836,897	€84,278,228	-2%

ASSETS

The gross value of fixed assets at end-2021 totaled **€27.9 million** (compared with **€26.9 million** at end-2020), including **€17.8 million** worth of laboratory equipment.

The value of fixed assets remained stable year on year. Since 2020, the amount includes an endowment contract held by the Foundation for an amount of €3.7 million (for the purpose of ring-fencing the non-expendable portion of the endowment) and non-financial assets.

Intangible fixed assets and property, plant and equipment

The net value of property, plant and equipment (€5.6 million versus €6.5 million in 2020) has decreased because amortization and depreciation charges exceeded acquisitions for the year. The amount of intangible assets increased over the same period (€74k versus €36k in 2020) due to the acquisition during the year of software for tracing biological samples (ModulBio).

Intangible fixed assets and property, plant and equipment for the year amounted to €1 million. The main acquisitions concerned deployment of the neuro behavior platform, the purchase of storage racks used in Animal care, the ModuleBio software mentioned above and refurbishment of part of the seminar center using funds from the Bettencourt Schueller Foundation.

The main building work carried out comprised various maintenance work on the building and the upkeep of infrastructure.

Financial fixed assets

Financial fixed assets were unchanged year on year at **€4.23 million** and comprised:

- €505k for the equity interest in Step Pharma,
- €3.7 million for the endowment contract, and

- €0.8k for shares held in SmartImmune, Medetia and Co- doc.

No new impairment expense was recognized in 2021.

Receivables

Accounts receivable amounted to €5.25 million (compared to €6.14 million in 2020), a decrease of €0.9 million. This decrease related to both overdue trade receivables and a decrease in unbilled revenue.

As in 2020, unbilled invoices essentially cover the building contributions of the founding members as well as amounts receivable from APHP-Necker for the reimbursement of operating costs for the hospital part of the building for the last three financial years. These amounts are currently being readjusted. None of these receivables is considered to be at risk and they have already been reduced.

Other receivables amounted to €47.6 million (versus €46.48 million in 2020) and consist mainly of accrued income on all public and private multi-annual agreements in progress for contractualized income to be paid in future periods. Public grants receivable amount to €41.5 million (versus €40.5 million in 2020), including €14.5 million in *PIA-IHU* funding, €10.6 million for *RHU* programs 3 and 4, €6.5 million for the DIM Gene Therapy program, €5.1 million for ANR generic project tenders awarded to *Imagine* teams (versus €2.6 million in 2020) and €1.5 million in EU funding. Private contributions receivable amount to €2.1 million (versus €2.7 million in 2020), including the Devodecode project funded by MSD Avenir.

Marketable securities

Marketable securities were stable year on year at €11.2 million and comprised year-end term account balances and CIC and Prêt d'Union securities.

There was a slight decrease in cash and cash equivalents - which now include current accounts and passbook accounts - from €9.7 million at the end of 2020 to €9 million at end-2021, as the Institute's banks are encouraging it to limit cash balances by at least placing them in term accounts. New ways of diversifying the manner in which cash balances are invested are currently being reviewed.

FUNDS AND LIABILITIES

Own funds

The Foundation's own funds comprise its initial endowment, reconstituted in full for an amount of **€12.9 million** at end-2017, cumulative retained earnings amounting to **€3.103 million**, and surplus income for 2021 (**€2.549 million**) along with investment subsidies received by the Foundation (for a net value of **€3.457 million**).

Own funds therefore total **€22.011 million** (versus €20.145 million in 2020).

Own funds increased significantly in 2021 thanks to recognition of the surplus for 2020 combined with operating income of €2.5 million in 2021, of which €1.1 million will have to be ring-fenced in off-balance sheet items for contribution margins on closed industrial contracts.

Loss and contingency provisions

As regards provisions for **charges**, the provision for retirement indemnities decreased to **€292k** in 2021, compared to **€328k** in 2020, due to the combined impact of an additional provision of 45k€ recorded for length of service on current employment contracts, and reversal of a provision for €81k due to the departure from the Institute of employees who had been working there for several years. The method used to account for the provision was unchanged from previous years.

Concerning provisions for **contingencies**, a provision for taxes totaling **€702k** was recognized in 2016 for a VAT tax audit covering fiscal years 2013 to 2016. As no decision has been handed down since that date, the provision has not been adjusted. Proceedings are still in progress and the provision was therefore maintained in 2021.

Dedicated funds

Pursuant to new accounting regulation No. 2018-06, dedicated funds correspond to the liability at year end that records the portion of resources allocated by third-party funders to defined projects in progress, in accordance with the commitment made to them, the unused balance of which must be ring-fenced in the accounts.

They amount to **€2.95 million** at the end of 2021, compared to €2.36 million at end-2020. Dedicated funds now comprise three blocks of financing: non-time limited public subsidies, non-time limited financial contributions and financing related to public generosity. The increase was mainly concentrated in the last category: year-end commitments that had not been fully deployed from a scientific perspective in 2021 (for the 'Tête et Cœur' program, Neurodevelopment, the Cross Lab program and research into DYS pathologies).

Liabilities

Liabilities amounted to **€56.882 million** compared to €60.71 million in 2020.

The decrease reflects the drop in deferred income from €53.652 million in 2020 to €48.752 million in 2021, notably due to the consumption of a significant portion of PIA-IHU funding in 2021.

Accounts payable increased from €4.541 million to €5.118 million due to an increase in unbilled payables, mainly attributable to payments to partners under the DIM Gene Therapy program (€920k).

There was a surplus of income over expenditure of **€2,549,469** in 2021 compared to a surplus of **€3,016,794** in 2020 (€122k in 2019 and €970k in 2018).

2021 income

Income jumped by 10% in 2021.

It has grown from €10 million in 2014 to €16.8 million in 2016, then €18.3 million in 2017. It reached €22.98 million in 2018, €26.69 million in 2019, **€27.01 million in 2020 and finally €29.6 million in 2021.**

Operating income	2021		2020		Δ 2021/2020	
	€	% Total	€	% Total	€	%
REVENUE	€2,283,250	8%	€2,305,721	9%	(€22,471)	-1%
OPERATING GRANTS	€15,298,571	56%	€10,995,603	43%	€4,302,968	39%
FINANCIAL CONTRIBUTIONS	€2,592,371	10%	€1,671,286	7%	€921,085	55%
EXPENSE TRANSFERS	€1,472,516	5%	€1,380,804	5%	€91,712	7%
DONATIONS AND PUBLIC GENEROSITY	€3,045,485	11%	€2,063,118	8%	€982,367	48%
OTHER OPERATING INCOME	€58,840	0%	€17,477	0%	€41,363	237%
<i>Sub-total, excluding revenue</i>	<i>€22,467,783</i>	<i>83%</i>	<i>€16,128,288</i>	<i>64%</i>	<i>€6,339,495</i>	<i>39%</i>
TOTAL OPERATING INCOME (EXCL. DEDICATED FUNDS CONSUMED)	€24,751,033	91%	€18,434,008	73%	€6,317,025	34%
USE OF DEDICATED FUNDS	€2,368,660	9%	€6,920,193		(€4,551,533)	-66%
TOTAL OPERATING INCOME	€27,119,693	100%	€25,354,201	100%	€1,765,492	7%

Operating income totaled €9 million in 2014, €14.8 million in 2015, €18.9 million in 2018, €17.04 million in 2019 and €25.35 million in 2020, before reaching **€27.119 million** this year despite the dual impacts of the economic and health crisis and postponement of the Heroes charity gala.

This **increase is mainly attributable to operating grants**, which amounted to €15.3 million in 2021, compared to €11 million in 2020 and €9.3 million in 2019.

Operating income therefore rose sharply (by 7%, and by 34% after neutralizing the use of dedicated funds whose accounting treatment leads to a distortion) and reflects the following:

- a big increase in public grants both from PIA-IHU funding and from Institut Carnot (+€1.8 million) and other public grants (+€2.5 million, again driven by the DIM TG program (+€0.5 million) and by AAP ANR (+€1.5 million)),
- a sharp drop in amounts recovered from dedicated funds from €6.92 million to €2.948 million, resulting from the application of the new accounting regulation in 2020 (dedicated funds recovered in 2020 still included significant amounts now recorded in deferred income for public grants and multi-year financial contributions, including PIA-IHU funding),
- a big increase in resources linked to public generosity (€1 million, despite the cancellation of the Heroes Gala in 2021),
- strong momentum in consumption of financial contributions (+€1 million),
- stable consumption of funding from industrial contracts.

Services sold correspond to **industrial and clinical research** contracts (€1.3 million versus €1.5 million in 2020), fees for hosting industrial projects (€0.32 million versus €0.27 million in 2020) and platform services (€0.64 million versus €0.4 million in 2020).

The **pandemic halted the uninterrupted growth**

recorded over the past five years, from €1.2 million in 2015 to €12.46 million in 2017 and €2.93 million in 2019; they amounted to €2.3 million in 2020 and 2021.

Although amounts billed for the year were lower than expected, the momentum of industrial partnerships (€1.1 million in 2016, €1.7 million in 2017, €1.9 million in 2018, €2 million in 2019, €0.7 million in 2020 and €2 million in 2021) is not encumbered by deferred income to be credited to 2021 for an amount of €2.6 million (versus €2.9 million in 2020).

There was a **big year-on-year increase in donations** (€3.045 million versus €2.063 million in 2020) although the total was below the amounts raised in 2019 (€3.325 million) and 2017 (€3.34 million).

Resources related to donations, philanthropy and financial contributions from non-profits remained stable due to the increase in donations from private individuals (impact of the major donor campaign and direct marketing) as well as from associations and foundations, which increased significantly (by €1.9 million, from €3.7 million to €5.6 million).

As in 2020, **financial contributions** include contractualized funding from foundations and associations previously recorded as donations or grants, amounting to €2.6 million, compared to €1.7 million in 2020. They are driven by all major components within this income category.

Financial income increased marginally in 2021.

In a sluggish money market, **interest and similar-type income** decreased once again (€20k in 2021, compared to €24k in 2020, €33k in 2019, €73k in 2018, €91k in 2017, €45k in 2016, €51k in 2015 and €71k in 2014).

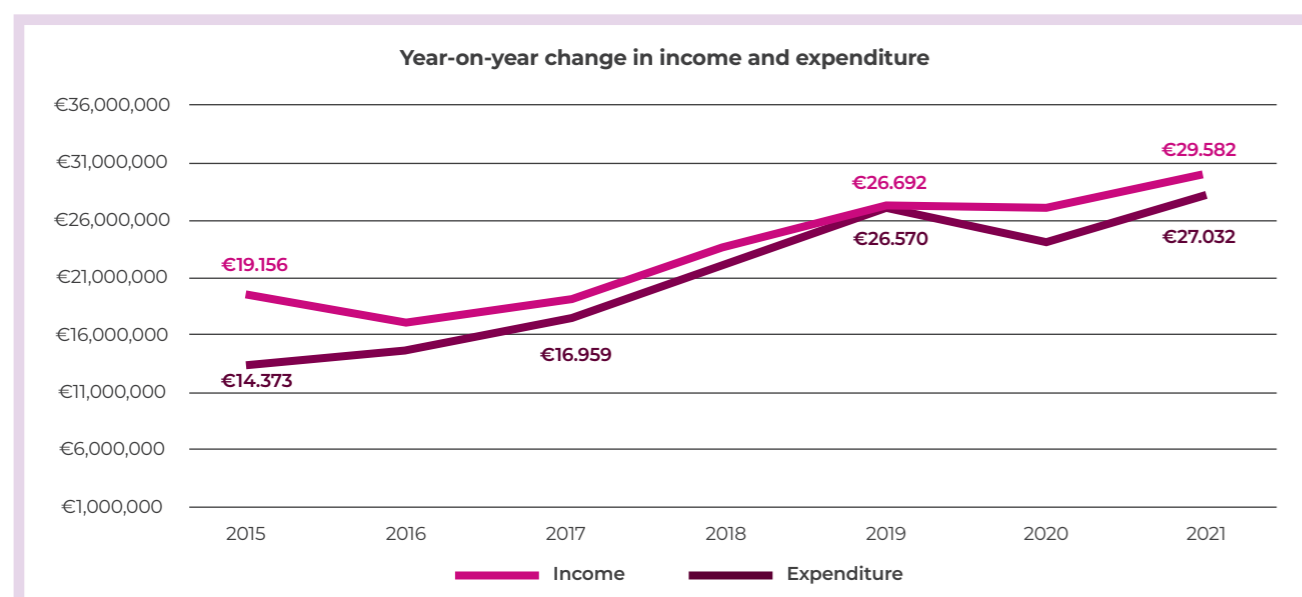
Our financial income balance does not just include interest and similar-type income. **Unrealized capital gains** not yet recognized on other financial income and not yet recorded in the accounts represent significant amounts (€895k in 2021, compared to €837k in 2020 and €781k in 2019).

2. Income statement

The 2021 income statement summarizes all flows that positively or negatively impacted *Imagine's* financial position in 2021, i.e., the income that generates wealth and the expenditure that reduces it by enabling the Institute to pursue its activities.

Imagine's income statement may be presented as follows:

	12/31/2021	12/31/2020	%
TOTAL INCOME	€29,582,212	€27,011,907	10%
TOTAL EXPENDITURE	€27,032,743	€23,995,112	13%
SURPLUS INCOME	€2,549,469	€3,016,795	-15%



Financial income increased due to positive exchange rate differences over the year; this item is cyclical.

The Institute's healthy cash and liquidity position provides it with the management agility needed to maintain the pace of project development. In late 2020, the Institute initiated an in-depth review in order to prepare a sub-annual control plan capable of identifying any additional investment potential. This plan must be combined with a multi-annual cash management plan to meet significant new cash flow challenges (advance payment of grants and contracts before the final report is prepared - many grants and contracts are expected to be finalized over the next two years - an increase in the number of grants that include advance cash payments, such as the DIM or certain EU grants, together with ever larger disbursements due to the considerable increase in the Institute's activities and research programs).

Operating expenses

	2021		2020		2021/2020	
	€	% Total	€	% Total	€	%
GOODS PURCHASED FOR RESALE	€2,492,184	10%	€1,642,019	7%	€850,165	52%
OTHER PURCHASES AND EXTERNAL CHARGES	€5,834,916	22%	€5,910,895	25%	(€75,979)	-1%
FINANCIAL AID	€2,983,755	11%	€2,617,870	11%	€365,885	14%
TAXES AND SIMILAR LEVIES	€418,269	2%	€331,401	1%	€86,868	26%
WAGES AND SALARIES	€6,760,102	26%	€6,497,556	27%	€262,546	4%
PAYROLL CHARGES	€2,549,830	10%	€2,427,803	10%	€122,027	5%
AMORTIZATION AND DEPRECIATION EXPENSE	€1,925,331	7%	€2,229,366	9%	(€304,035)	-14%
ADDITIONS TO (REVERSALS OF) PROVISIONS	- €	0%	€54,906	0%	(€54,906)	-100%
TRANSFERS TO DEDICATED FUNDS	€2,948,570	11%	€1,724,295	7%	€1,224,275	71%
OTHER CHARGES	€237,312	1%	€192,956	1%	€44,356	23%
TOTAL OPERATING EXPENSES	€26,150,270	100%	€23,629,067	100%	€2,521,203	11%
TOTAL OPERATING EXPENSES LESS TRANSFERS TO DEDICATED FUNDS	€23,201,700	89%	€21,904,772	93%	€1,296,928	6%

The increase in expenditure was driven by **growth in hosted contracts** funded out of public grants or research partnerships with the socio-economic sphere, which represent 42% of the total budget (an increasing proportion) and grew by €1.5 million (+19%), including €0.6 million for payments to consortium partners involved in RHU and DIM funding.

The biggest growth was in the **launch of new calls for projects**, i.e. the 32 projects selected in 2020 and 2021 following the ANR's generic call for tenders (+€0.8 million) and completion of cross-cutting projects such as the DIM Gene Therapy program (+€0.9 million), projects funded by the European Commission (+€213k), and the RHU 4 Attraction project (+€329k). Expenditure on financial contributions was especially dynamic (+€210k, notably on the Cystinosis Research Foundation - Foundation for Medical Research).

Non-recurring income totaled **€2.428 million**, compared with €1.632 million in 2020 and €696k in 2019, comprising two distinct components:

- the first is made up of the share of investment grants previously recognized in liabilities (€1.3 million in 2021 versus €1.622 million in 2020),
- the second concerns the correction of one-off errors (€1.1 million) on industrial contracts.

2021 expenditure

The **Institute's total expenditure** rose by **13%** in 2021 to **€27.032 million**, compared to €23.99 million in 2020, €26.57 million in 2019, €16.6 million in 2017, €14.8 million in 2016 and €14.4 million in 2015. It may be broken down into operating expenses, financial expenses and non-recurring expenses.

Operating expenses totaled **€26.150 million**

in 2021, compared to €23.62 million in 2020, €19.54 million in 2019, €17.1 million in 2018, €13.8 million in 2017, €12.9 million in 2016 and €10.4 million in 2015.

This momentum was directly reflected in the **€0.4 million** year-on-year increase in **personnel costs** (+4% on average, +9% on hosted contracts, +29% on platforms).

The Foundation employed **163.7 FTEs** at 12/31/2021 (excluding people on secondment, volunteers, apprentices, interns and hosting arrangements), approximately the same number of FTEs as at 12/31/20 and 12/31/19.

Consumables and services increased by 9%, driven by expenditure on hosted contracts (+€0.5 million, or +19%) as well as single cell and genomic platforms (+€0.2 million).

Payments to consortium **partners** involved in RHU and DIM funding increased significantly for the third year in a row (€2.9 million, compared to €2.6 million in 2020 and €1.3 million in 2019). A major part of these payments is related to the DIM TG project (including €920k for invoices not yet issued by our partners).

Amortization and depreciation expense was lower in 2021 (€1.9 million compared to €2.2 million in 2020 and 2019). As a result of limited acquisitions made during 2021, the wear and tear rate in 2021 was significantly higher than in 2020, rising from 71% to 76%. This phenomenon affects all of the Institute's asset categories. Certain major asset renewals are expected over the coming years (3T MRI and cryogenic tanks in 2023, for example). A multi-year equipment plan will be submitted to the Governing Board along with the budget forecast as major challenges await in 2023.

Non-recurring expenses correspond to accounting adjustments and varied by **€511k** between 2020 and 2021 due to the correction of three errors:

- an adjustment for the **audit performed by the French National Research Agency (ANR) on eligible and declared expenses for PIA IHU funding in 2020** for an amount of €403k,
- a correction to reconstitute **deferred income for clinical research studies** which had not been performed in previous years following specific internal reviews still in progress on these studies, amounting to €384k, and
- reconstitution of **investigator credits for reference centers for rare diseases (€81k)** had only been ring-fenced in off-balance sheet items. They have been reconstituted in the accounts to enable the managers of the centers to use them.

The **result** for the year is therefore a surplus of income over expenditure of **€2.549 million** (compared to €3.017 million in 2020).

Income and expenditure by source and use

	2021		2020	
	TOTAL	o/w raised from public generosity	TOTAL	o/w raised from public generosity
INCOME BY SOURCE				
DONATIONS, BEQUESTS AND PHILANTHROPY	€3,045,485	€3,045,485	€2,063,118	€2,063,118
- INDIVIDUAL DONATIONS	€2,395,299	€2,395,299	€1,413,118	€1,413,118
- DONATIONS, BEQUESTS AND LIFE INSURANCE	€10,185	€10,185	€	€
- PHILANTHROPY	€640,000	€640,000	€650,000	€650,000
INCOME NOT RAISED FROM PUBLIC GENEROSITY	€7,520,384		€5,480,678	
FINANCIAL CONTRIBUTIONS GIVEN WITHOUT RECEIPT OF ANY SPECIFIC CONSIDERATION	€2,592,371		€1,671,286	
OTHER INCOME NOT RAISED FROM PUBLIC GENEROSITY	€4,928,012		€3,809,392	
GRANTS AND OTHER PUBLIC FUNDING	€16,595,942		€12,547,918	
RELEASE OF PROVISIONS, AMORTIZATION AND DEPRECIATION	€51,743		€	
USE OF DEDICATED FUNDS BROUGHT FORWARD	€2,368,660	€851,004	€6,920,193	€799,309
TOTAL	€29,582,21	€3,896,489	€27,011,907	€2,862,427
EXPENDITURE BY USE				
SOCIAL MISSIONS	€20,995,582	€2,165,130	€19,401,404	€1,505,695
- ACTIONS PERFORMED BY THE INSTITUTE	€18,011,827	€2,165,130	€16,783,534	€1,505,695
- PAYMENTS TO A CENTRAL BODY OR TO OTHER BODIES OPERATING IN FRANCE	€2,983,755		€2,617,870	
2 - FUND-RAISING EXPENSES	€1,063,077	€120,285	€892,327	€83,650
2.1 COST OF RAISING FUNDS FROM PUBLIC GENEROSITY	€924,305	€120,285	€784,463	€83,650
2.2 OTHER FUND-RAISING EXPENSES	€138,772		€107,865	
3 - OPERATING EXPENSES	€2,025,514	€120,285	€1,922,181	€83,650
4 - ADDITIONS TO PROVISIONS, AMORTIZATION AND DEPRECIATION EXPENSE	€		€54,906	
6 - TRANSFERS TO DEDICATED FUNDS OVER THE PERIOD	€2,948,570	€1,490,789	€1,724,295	€851,004
TOTAL	€27,032,743	€3,896,489	€23,995,112	€2,523,998
SURPLUS OR (DEFICIT)	€2,549,470	- €	€3,016,795	€338,428

Excluding the two non-recurring items for the year (correction of errors on income (€1.1 million on contribution margins on closed industrial contracts) and on expenses (€0.9 million)), the surplus for the year would have been €2.3 million, well above the forecast of €0.3 million presented at the December 2021 Governing Board meeting. The forecast had been presented as a conservative one, especially with regard to recognition of financial contributions, which ultimately turned out to be more than satisfactory, and due to the non-occurrence of certain management contingencies that had also been included as a precautionary measure but did not actually materialize.

3. Annual funds flow statement

For the second year, we are presenting a statement of sources and uses of funds, and for the ninth consecutive year, an annual funds flow statement showing the allocation of resources raised from the public by type of use, to enable *Imagine's* donors and patrons to track how donations contribute to scientific projects. This new accounting treatment is detailed in the notes to the accounts.

STATEMENT OF SOURCES AND USES OF FUNDS

89% of funds are used for social missions, 4% for fund-raising expenses and 7% for various operating costs.

PRESENTATION OF SOURCES

Sources collected from the public, for a total of **€3,045,485** (versus **€2,063,118** in 2020), are composed of three lines:

- individual donations, totaling **€2,395,299** (versus **€1,413,118** in 2020),
- philanthropy, for a total of **€640,000** (Axa funding of the *Tête et Cœur* Chair and various donations for research into DYS pathologies, and the final tranche of funding for the Dior 1 Chair) compared to €650,000 in 2020 (for Dior 1 Chair funding in 2020 and 2021).

Income not raised from public generosity comes from three sources:

- **grants and other public funding**, mainly comprising IHU funding and other public grants from the ANR and the Greater Paris Region for an amount of **€16,565,942** (versus **€12,547,918** in 2020).
- **financial contributions** for a total amount of **€2,592,371** (versus **€1,671,286** in 2020). These now include all funding from associations, endowments and foundations,
- **other income not raised from public generosity** for an amount of **€4,928,012** (versus **€3,809,392** in 2020).

Total sources for the period recorded in the income statement amounted to **€27,213,553** (versus **€20,091,714** in 2020) plus unused allocated resources brought forward from previous years totaling **€2,368,660** (versus **€6,920,193** in 2020), giving a grand total of **€29,582,213** (versus **€27,011,907** in 2020).

PRESENTATION OF USES

Uses amount to **€27,032,743** (compared to **€23,995,112** in 2020). The statement of sources and uses of funds presents the surplus generated, correlated in particular to the corrections made to previous years. The funds flow statement does not present a surplus.

Total outflows of funds were used as follows:

- **89%** on social missions (including reconstitution of dedicated funds) versus 88% in 2020,

- **4%** on fundraising expenses, which are now divided into two lines (costs of raising funds from public generosity for 3%, and other fund-raising costs for less than 1%), unchanged from 2020,

- and **7%** across all operating expenses (versus 8% in 2020).

Social missions (excluding dedicated funds) totaling **€20,995,582** (compared to **€19,401,404** in 2020) is obtained by restating uses for the year recorded in the income statement and allocated to social missions.

FUNDS FLOW STATEMENT

Since 2020, the funds flow statement no longer includes the financial contributions of private non-profits previously included in resources raised from public generosity.

94% of funds are used for social missions (including the constitution of dedicated funds), 3% for fund-raising costs and 3% for all types of operating costs. No surplus resources were recorded in relation to public generosity.

Donations collected in 2021 amounted to €3,045,485 (compared to €2,063,118 in 2020) and are rounded out by a €799,308 increase in dedicated funds corresponding to the recovery of donations collected in previous years. Consequently, sources collected from the public and used in 2020 total €2,523,998 and may be broken down into:

- a. social missions: €2,165,130 (56%) versus €1,505,694 (60%),
- b. constitution of dedicated funds used for social missions: €1,490,789 (38%) versus €851,004 (32%),
> i.e., a total of (94%) for all social missions allocated over this year and coming years
- c. costs of raising funds from public generosity: €120,285 (3%), compared to €83,650 (3%),
- d. operating expenses: €120,285 versus €83,650 (3%),
> Fund-raising and operating expenses are calculated based on social missions charged during the year and not on dedicated funds.

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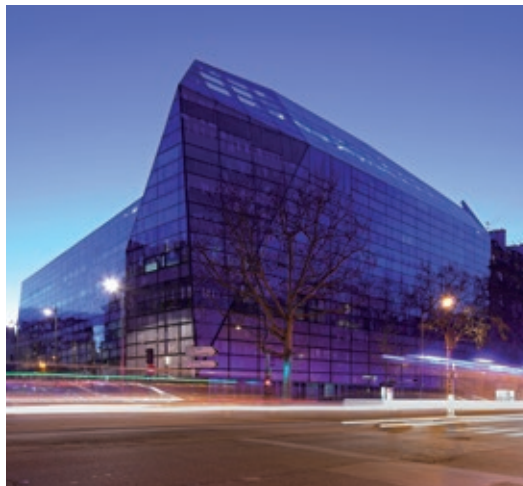
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