ACTIVITY REPORT 2019

IMAGINE, CURING GENETIC DISEASES

imagine

INSTITUTE FOR GENETIC DISEASES

HISTORY

IMAGINE

2007

Creation of the *Imagine* Foundation by its founding president Claude Griscelli. Six founding members: AP-HP *(Paris Public Hospitals Group), Inserm, Paris Descartes University (now Université de Paris), Paris City Council, AFM-Téléthon and Hospitals of Paris-Hospitals of France Foundation.*

2008

1st recruitment,
1st platforms and
1st equipment.

2009

Creation of the *Imagine* International Scientific Advisory Board, chaired by Prof. Elizabeth Blackburn, 2009 Nobel Prize in Medicine.

2011

IHU (University Hospital Institute) label awarded as part of the Investments for the Future Program.

2012

1st recruitment
of international teams.

2014

Inauguration of
the *Imagine* building.

2015

First *Heroes* Gala for the *Imagine* Institute and held on its premises, followed by new editions in 2016 and 2018.

2016

Prof. Stanislas Lyonnet succeeds Prof. Alain Fischer as director of *Imagine*, and Prof. Arnold Munnich succeeds Prof. Claude Griscelli as president of the *Imagine* Foundation.

2017

Launch of the RHU C'IL-LICO project: 'Medicine of the Future for Ciliopathies with Renal Involvement.'

Major Field of Interest (DIM) label in Gene Therapy, funded by the Ile-de-France region.

2018

Assessment of the Institute's 24 research laboratories by HCERES (High Council for Evaluation of Research and Higher Education).

A total of 25 reference centers for rare diseases on the Necker-Enfants malades Hospital campus affiliated to *Imagine*, as well as four associate laboratories.

2019

Launch of the RHU ATRACTion project: 'Primary immunodeficiency with autoimmunity or autoinflammation.'

Success of the ANR-PIA (Investments for the Future Program) call for projects to extend the IHU label until 2024.

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EDITORIAL

CROSS INTERVIEWS

2019 was a key year for *Imagine*, once again awarded the University Hospital Institute label.

Stanislas Lyonnet, director of the *Imagine* Institute: 2019 was a crucial year for the future of *Imagine* in terms of conducting its projects for the next ten years. Following an assessment conducted to the highest requirements by international experts, relating to the '*Imagine* 18–28' roadmap, Prime Minister Édouard Philippe decided to extend *Imagine*'s University Hospital Institute (IHU) label as part of the Investments for the Future Program (PIA). Funding of €17 million has therefore been allocated by the National Research Agency (ANR) to the Institute until 2024. The expert committee confirmed *Imagine*'s place as 'world leader in genetics and the treatment of rare genetic diseases.' This decision reflects the recognition of the quality of the work undertaken by our teams since the creation of the Institute, and our ability to develop an effective innovation ecosystem; by clearly understanding the 'I' in PIA as a genuine 'investment' and, therefore the firm intention of giving all value to science linked to medicine together, these two, often only appearing on the expenditure line in the French Nation's accounts. However, other major successes have accompanied the progress of *Imagine* this year, from the success of *Imagine*'s project on immune deficiencies (ATRACTion) to the University Hospital Research (RHU) call, another aspect of the PIA.

Laure Boquet, general delegate of the *Imagine* Institute: We would like to thank our public and private founding members, as well as our partners and patrons, who have strongly supported us in this candidacy, both showing their confidence and working alongside us to deploy our strategic projects – they were again great in their support and actions during the exceptional crisis due to the Covid-19 epidemic we are going through at the time of writing this. This extension of the IHU label also rewards them, the public and private friends of *Imagine*, by giving the Institute the opportunity to pursue its ambitions for the benefit of sick children. Through this new commitment, *Imagine* has led breakthrough projects such as the creation of a data center, a financial accelerator, the 'Lab-in-Labs' hosting facility, the extension of its scientific and bioinformatics reception capacities, and the development of an integrative social program in human and social sciences.

2019 was also a year of openness and international collaboration

Arnold Munnich, president of the *Imagine* Foundation: To change the lives of families affected by genetic diseases, to remain at the forefront of advances in genetics, to produce the best science, and to promote its discoveries, *Imagine* must collaborate internationally. By attracting talent from the world over and spreading knowledge, and also by carrying out collaborative European or global projects. 2019 was a wonderful illustration of this, with the launch of international projects bringing new hopes in therapeutic research for families. This openness is also illustrated by the Institute's involvement in major European projects such as HDM-FUN, on invasive fungal infections, and BIND, to improve knowledge on Duchenne and Becker muscular dystrophy; and in two European training networks: SCils on ciliary signaling during normal and pathological development, and NEUcrest on the neural crest.

Laure Boquet : Our opening up to the Necker-Enfants malades Hospital campus, to the medical community, to patient associations, and also simply to our city and Parisians, is essential and is continuing. In 2019, we continued to host dedicated seminars and we participated in major regional and national plans and projects on genetic diseases and rare diseases, such as the European Joint Program on Rare Diseases. *Imagine* was keen to support events dedicated to patient associations, such as the Eurordis Winterschool or the very first European meetings for families affected by diseases associated with KCNB1 Mutations. For a more human vision of pediatric genetics and precision genomics, *Imagine* has worked on the deployment of a social and human sciences program, with the launch of a call for projects which selected three projects with the aim of improving the quality of life of patients.

What is the biggest challenge for *Imagine*?

Stanislas Lyonnet: The 'virtuous loop' model of *Imagine*, i.e., from care to research, then from research to care, always involves the accurate diagnosis of children and families affected by genetic diseases, which is very often difficult, with diagnostic delay or even diagnostic impasse. Today, one in two children still has no diagnosis. Genetic testing, increasingly effective, can lead to a difficult and lengthy interpretation. Here, paradoxically, is one of the greatest challenges of modern genetics: the easier it is to obtain genetic data, the more complex its interpretation! This is a huge question, but we are convinced that there is no glass-ceiling set at 40% for diagnosing children with genetic diseases. Our ambition is to double this proportion by 2028. To achieve this, *Imagine* is brimming with the best clinical, genomic, bioinformatic and artificial intelligence talent, and has, at the time of writing this report, two necessary accelerators: the IHU label guaranteeing the practice of the best science of today to invent the best medicine of tomorrow; and the Carnot Institute label, that *Imagine* recently obtained with a view to maximizing the value of its research. They are both essential to our mission: to change the lives of families affected by genetic diseases.

A word from Claude Griscelli, founding president of Imagine :

Five years have already passed since the creation of Imagine*: enough to ascertain its values. There is no doubt about the importance of the cause: understand in order to relieve. It has become a motto that unites teams and makes them strong. Wonderful research results that make it possible to fight genetic diseases better! New hopes for some of them! But so much remains to be done, the task is immense. Let us be as confident as we are proud.*

KEY FIGURES

2019

1,000
RESEARCH AND HEALTH STAFF GATHERED AROUND THE SAME CAUSE

24
BASIC AND TRANSLATIONAL RESEARCH GROUPS ON SITE

16
CORE FACILITIES

4
ASSOCIATED LABORATORIES AT NECKER-ENFANTS MALADES HOSPITAL

862
SCIENTIFIC PUBLICATIONS (IHU PERIMETER)

37
NATIONALITIES

31%
OF PHD STUDENTS, POST-DOCS AND STUDENTS

MORE THAN
30,000
CONSULTATIONS ON SITE

6
INTEGRATED CARE AND RESEARCH PROGRAMS (iCARPs)

25
AFFILIATED REFERENCE CENTERS FOR RARE DISEASES

6
AFFILIATED HOSPITAL UNITS

2
CLINICAL INVESTIGATION CENTERS

544
ONGOING CLINICAL STUDIES IN THE IHU PERIMETER

NEARLY
140,000
SAMPLES (BIOLOGICAL RESOURCE CENTER)

55
ACTIVE PATENTS AND PROPRIETARY SOFTWARE PROGRAMS

NEARLY
3 M€
BY INDUSTRIAL PARTNERSHIP CONTRACTS WON IN 2019

NEARLY
4 M€
RAISED (GIFTS, GRANTS AND PHILANTHROPY)

6
RUNNING ERC (EUROPEAN RESEARCH GRANTS), INCLUDING 2 CONSOLIDATOR ERC

IMAGINE'S FOUNDING MEMBERS:

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Inserm
La science pour la santé
From science to health

Université de Paris

FONDATION Hôpitaux de Paris Hôpitaux de France
Reconnue d'utilité publique
Mieux vivre l'hôpital, c'est aussi guérir.

MAIRIE DE PARIS

AFM TÉLÉTHON
INNOVER POUR GUÉRIR

iCARPs (INTEGRATED CARE AND RESEARCH PROGRAMS), RESEARCH AND CARE ACCELERATORS

HEMATOLOGY

RESEARCH LABORATORIES

- Human lymphohematopoiesis ▸ **I. André**
- Molecular mechanisms of 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**

NECKER-ENFANTS MALADES CLINICAL UNITS

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

NEURO-DEVELOPMENT

RESEARCH LABORATORIES

- Developmental Brain Disorders ▸ **V. Cantagrel**
- Translational research for 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 LABORATORIES

- Image@*imagine* Multimodal brain imaging research ▸ **N. Boddaert**

REFERENCE CENTERS FOR RARE DISEASES

- Intellectual disabilities of rare causes ▸ **M. Rio**
- DI-Rett center ▸ **N. Bahi-Buisson**
- Rare ophthalmological diseases ▸ **D. Brémond-Gignac**
- Hereditary metabolic diseases ▸ **P. de Lonlay**
- Mitochondrial diseases ▸ **JP. Bonnefont**
- Rare epilepsies ▸ **R. Nabbout**

IMMUNOLOGY-INFECTIOLOGY

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 susceptibility to EBV ▸ **S. Latour**
- Inflammatory responses and transcriptomic networks in diseases ▸ **M. Ménager**
- Molecular basis of altered immune homeostasis ▸ **G. Ménasché & F. Sepulveda**
- Immunogenetics of pediatric autoimmune diseases ▸ **F. Rieux-Laucat**
- Genome dynamics in the immune system ▸ **JP. de Villartay & P. Revy**

REFERENCE CENTERS FOR RARE DISEASES

- Hereditary immune-deficiencies ▸ **A. Fischer**
- Rare digestive tract diseases ▸ **O.Goulet**
- Juvenile arthritis ▸ **P. Quartier dit Maire**

NECKER-ENFANTS MALADES CLINICAL UNITS

- Pediatric immuno-hematology and rheumatology ▸ **S. Blanche**
- Infectious and tropical diseases ▸ **O. Lortholary**

NEPHROLOGY

RESEARCH LABORATORIES

- Laboratory of hereditary kidney diseases ▸ **S. Saunier & C. Antignac**
- Epithelial biology and diseases ▸ **M. Simons**

REFERENCE CENTERS FOR RARE DISEASES

- Hereditary kidney diseases of the child and the adult ▸ **R. Salomon**

NECKER-ENFANTS MALADES CLINICAL UNITS

- Nephro-transplantation ▸ **C. Legendre**
- Pediatric nephrology ▸ **R. Salomon**

Alessandra Pierani's team

DEVELOPMENT & CARDIOLOGY

RESEARCH LABORATORIES

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

ASSOCIATED LABORATORIES

- Molecular basis of several congenital or neonatal endocrine disorders and establishment of therapeutic strategies ▸ **M. Polak**
- IMAG2 Computational anatomy for image-guided minimally invasive surgery in pediatric tumoral and developmental diseases ▸ **S. Sarnacki & I. Bloch (Télécom ParisTech)**

REFERENCE CENTERS FOR RARE DISEASES

- Pierre Robin Sequence ▸ **V. Abadie**
- Developmental abnormalities and malformation syndromes ▸ **J. Amiel**
- Genetic diseases with cutaneous expression ▸ **C. Bodemer**
- Complex congenital heart defects ▸ **D. Bonnet**
- Constitutional bone diseases ▸ **V. Cormier-Daire**
- Rare ENT malformations ▸ **F. Denoyelle**
- Genetic deafness ▸ **S. Marlin**
- Cranial and facial malformations ▸ **A. Picard**
- Rare gynecological pathologies ▸ **M. Polak**
- Rare anorectal and pelvic anomalies ▸ **S. Sarnacki**
- Craniosynostosis ▸ **M. Zérah**
- Vertebral and spinal malformations ▸ **M. Zérah**

COMPUTATIONAL DECISION-SUPPORT SYSTEMS

RESEARCH LABORATORIES

- Clinical bioinformatics ▸ **A. Rausell**

NECKER-ENFANTS MALADES CLINICAL UNITS

- Mecidal Genetics Federation ▸ **JP. Bonnefont**
- Medical informatics ▸ **A. Burgun**

CLINICAL AND TECHNOLOGICAL BASE

2 CLINICAL INVESTIGATION CENTERS AT NECKER-ENFANTS MALADES HOSPITAL

- 1 multi-thematic mother-child center ▸ **JM. Tréluyer**
- 1 biotherapy center ▸ **M. Cavazzana**

SUPPORT PLATFORM FOR CLINICAL RESEARCH (*IMAGINE*)

- 1 investigation teamn
- 1 promotion team

16 CORE FACILITIES

- *Imagine* : Data Sciences, IPS (induced pluripotent cells), transgenesis, single-cell, rAAV
- SFR Necker / *Imagine* and founding members : Imaginge/IRM3T, genomics, bioinformatics, biological resource center, protéomics, cytometry, cell imaging, histology, viral vectors and gene transfer, animal facility, metabolomics.

OUR GOVERNANCE

The *Imagine* Institute is supported by a **Foundation for Scientific Cooperation (FCS)** created in 2007. This private structure makes it possible to manage both public and private funds. This status provides flexibility and responsiveness by combining the best of the public and private sectors, with the aim of accelerating research on genetic diseases.

Imagine was awarded the **University Hospital Institute (IHU) label** in 2011. In this context, the Institute is to receive an endowment allocated to it under the **Investments for the Future Program (PIA)** until 2020. In 2019, *Imagine* submitted its application to extend part of this grant until 2024. Following an assessment by a committee of international experts, the General Secretariat for Investment (SGPI, Matignon) and the French National Research Agency (ANR) decided to renew the Institute's IHU label and to allocate it funding of €17 million for the period 2020–2024.

Awarded the Tremplin Carnot label by the French Ministry of Higher Education, Innovation and Research in 2016, the Institute applied in 2019 for the **Carnot Institute label**. At the time of writing this report, we learn that *Imagine* has obtained this very competitive certification for the period 2020–2024, a mark of recognition for the quality and dynamism of its industrial relations and partnerships.

Our founding members

Imagine has been supported by six founding members since its creation. We thank them for the support and trust they give us every year.

- **AP-HP (Paris Public Hospitals Group)**
- **Inserm**
- **Université de Paris**
- **Hospitals of Paris-Hospitals of France Foundation**
- **Paris City Council**
- **AFM-Telethon**

Our governing bodies

The *Imagine* Foundation has a **Board of Trustees** composed of the six founding institutions and the qualified experts selected by them, as well as the elected representatives of the Foundation's teachers, researchers, doctor-researchers and employees.

The director of the Institute relies on a mixed **Management Committee** made up of researcher and clinician representatives from the various research and care programs conducted at *Imagine*.

The **IHU Board** brings together laboratory directors and staff representatives for the purpose of discussing the main scientific orientations and the organization of the running of the Institute.

INTERNATIONAL SCIENTIFIC ADVISORY BOARD

Composed of eminent world-renowned scientists, the International Scientific Advisory Board issues annual recommendations to the Board of Directors and *Imagine* management regarding the Institute's scientific and strategic orientations, including the selection of new teams, the development and organization of scientific groups and the assessment of their work. In 2019, this board convened at *Imagine* on October 21 and 22.

Composition of the Scientific Advisory Board

Prof. Elizabeth Blackburn
2009 Nobel Prize winner 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. Bernard Malissen
Center for Immunophenomics, Marseille-Luminy, France

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

Prof. Fiona Powrie
Kennedy Institute of Rheumatology, University of Oxford, United Kingdom

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

At the time of writing this report, a new member was invited to the board, **Prof. Douglas Higgs**, MRC Weatherall Institute of Molecular Medicine, University of Oxford, United Kingdom.

Two questions put to Elizabeth Blackburn, president of the International Scientific Advisory Board:

What have you taken away from this 2019 board meeting?

Once again, this year, the board's opinion is extremely positive: *Imagine* is growing and confirming its position as the international leader in medical genetics and human genomics. With the Necker Campus, *Imagine* combines high-level translational scientific and clinical research on childhood genetic diseases and their treatment, enabling well-targeted and continuous progress to be achieved.

Not only has gene discovery made great strides, but the translation of these strides into effective diagnostics and therapies for patients, including gene therapies, has been a game-changer.

What are the challenges for *Imagine*?

Science at *Imagine* must remain flourishing and vital. The Institute must look to the future and to those who will make the science and medicine of tomorrow, by attracting students and young researchers, by supporting them on their career journey, through teaching, mentoring and scientific emulation programs. We also encourage the Institute to recruit new junior teams, particularly in the field of neurogenetics.

In addition, the need for data storage, data sharing and dissemination policy decisions is increasing. The board supports investment in these areas and encourages *Imagine* to assume global leadership.

HIGHLIGHTS

Imagine's University Hospital Institute (IHU) label is renewed

Created as part of the Investments for the Future Program in 2011, IHUs are places of scientific and medical excellence in research, care, training and technology transfer. French Prime Minister Édouard Philippe wished to renew his confidence in this innovative model by entrusting the French National Research Agency with the assessment of these IHUs. In November 2019, it announced the extension of *Imagine*'s IHU label and five further IHUs for the period 2020–2024, with the allocation to *Imagine* of €17 million over this period.

The international jury highlighted the excellence of *Imagine*, which it described as a world leader in genetic research and treatment of rare genetic diseases, bringing together the best talent in this field: «This decision reflects the recognition of the quality of the work carried out since the creation of the Institute and our ability to develop an efficient innovation ecosystem", says Prof. Stanislas Lyonnet, director of *Imagine*.

ATRACTion: to better understand immune deficiencies

The ATRACTion project is one of the winners of the fourth 'University Hospital Research in Health' call for projects under the Investments for the Future Program. It brings together eleven partners, both academic in the case of Inserm, AP-HP, INRA, CEA and the Université de Paris, and industrial, in the case of Sanofi and Ariana Pharma.

«At present, we do not know how to distinguish between the various forms of primary immune deficiency, nor do we know how to anticipate their development or the risks involved. By using innovative technologies based on cell-by-cell analyses coupled with artificial intelligence, we want to be able to better diagnose these diseases, stratify them according to risks, develop kits to refine prognosis, offer an application to support healthcare professionals in their diagnostic and therapeutic decisions, and develop new therapeutic strategies. The originality of this project is to conduct analyses at the single-cell level, whilst analyzing the composition of the microbiota and metabolites the cell produces,» explains Frédéric Rieux-Laucat, project leader at *Imagine*.

Two projects awarded an ERC Consolidator Grant

In 2019, the European Research Council awarded a prestigious grant, the ERC Consolidator Grant, to two *Imagine* team leaders to enable them to consolidate their teams and research projects.

Thanks to this ERC grant, Annarita Miccio, director of the Laboratory of Chromatin and Gene Regulation During Development, will be able to accelerate the development of innovative therapeutic strategies for beta hemoglobinopathies, with, at the heart of her work, gene therapy and the exploration of base editing, a new approach that consists of modifying a letter of the genetic code without breaking it.

Matias Simons, director of the Laboratory of Epithelial Biology and Diseases, explores the mechanisms behind rare kidney diseases in order to better understand and treat them. This funding will enable him to develop a project on targeting tubular reabsorption as a renal protection strategy.

AWARDS AND REWARDS

- **Corinne Antignac**
  Appointed to the French Academy of Sciences
- **Meriem Belabed :**
  Winner of the *Imagine* Thesis Award
- **Marina Cavazzana :**
  Appointed to the US National Academy of Medicine
- **Jean-Laurent Casanova**
  2018 Claude Bernard Grand Prix of the City of Paris
  Thomas A. Waldmann Prize from the Foundation for Primary Immunodeficiency Diseases
- **Max Cooper** (former SAB member)
  2019 Albert Lasker Prize for Fundamental Medical Research
- **Alain Fischer**
  Appointed to the US Academy of Sciences
- **Chiara Guerrera**
  Inserm Innovation Prize
- **Emmanuelle Jouanguy**
  2019 Charles-Louis de Saulses de Freycinet Prize (French Academy of Sciences)
- **Gaspard Kerner**
  Winner of the Imagine Thesis Award
- **Mickaël Ménager**
  Emergence Funding Prize from the City of Paris
  2019 Delheim Prize from the Collège de France
- **Annarita Miccio**
  Sanofi iAwards Europe
  ERC Consolidator Grant
- **Géraldine Mollet**
  Sanofi iAwards Europe
- **Gayetri Ramachandran**
  Promega Young Researchers National Prize
- **Matias Simons**
  ERC Consolidator Grant

THE '*IMAGINE* 18-28' ROAD MAP

TO NAME AND CURE GENETIC DISEASES

Since the creation of the *Imagine* Foundation in 2007, *Imagine* has implemented many transverse and structuring projects, formalized in 2010 in its University Hospital Institute program and renewed in 2016 with its founding members, in a 2016–2025 strategic roadmap. In 2018, guided by the ambition to change the lives of families affected by genetic diseases, *Imagine* set new ambitions for the next ten years. These objectives were readjusted in 2019 as part of the submission to extend the label and to finance the Institute's Hospital-University Institute status for the period 2020–2024.

Taken separately, genetic diseases are very uncommon, even exceptional. But collectively, across Europe, they affect thirty million people. In France, three million people are affected, i.e., nearly one in twenty French people. In addition to this public health problem, nearly 50% of these diseases are undiagnosed, and when they are, it is most often after months or even years of diagnostic delay.

The power of *Imagine* is to be able to bring together in one place research and care teams, rare diseases reference centers, and clinical services at Necker-Enfants malades Hospital around patients. By bringing together all these players, *Imagine* creates the right conditions to go further and faster thanks to a unique 'loop' approach: clinical observation, analysis and understanding of the causes and mechanisms of diseases that encourage the discovery of new diagnoses, new treatments and their implementation.

Imagine, the first European research and care center for genetic diseases

Throughout its existence, *Imagine* has demonstrated its unique ability to accelerate research and innovation, both in terms of diagnosis and treatment. Since its creation, *Imagine* has:

- Conducted more than 30,000 consultations a year *in situ* and in reference centers
- Identified more than 250 genes, making it possible to hasten diagnosis
- Developed more than 32 clinical gene and exome panels that have enabled clinical diagnosis of more than 3,000 diseases
- Conducted world-leading therapeutic trials, be they for new therapies or for the repurposing of compounds already used for other diseases: sickle cell disease, beta-thalassemia, interferonopathy, achondroplasia
- Collected 50 million patient data points from 5.6 million documents, structured in a rare disease research repository, to facilitate advances and discoveries
- Identified 52 therapeutic solutions, at the clinical or preclinical stage
- Performed over 25,000 DNA sequences
- Included more than 7,000 patients in more than 580 clinical trials.

Priority research and care programs

To accelerate discovery and innovation for the benefit of patients, *Imagine* has identified priority areas for the coming years. Each of these areas (see pages 6 and 7) brings together research teams, technological platforms, associated laboratories, reference centers, and clinical services from the campus of Necker-Enfants malades Hospital.

SIX INTEGRATED CARE AND RESEARCH PROGRAMS (iCARPs) :

▸ DEVELOPMENT AND CARDIOLOGY ▸ HEMATOLOGY
▸ IMMUNOLOGY-INFECTIOLOGY ▸ ARTIFICIAL AND COMPUTATIONAL INTELLIGENCE
▸ NEPHROLOGY ▸ NEURO-DEVELOPMENT

Imagine 2028: changing the lives of families affected by genetic diseases

Imagine researchers and doctors are continuing their efforts and stepping-up their actions because much remains to be done to name diseases, understand them, and offer therapeutic solutions to affected children.

By 2028, the Institute has set itself the following objectives:

- Double the number of children diagnosed (by increasing the elucidation rate to 80%), and thus significantly reduce diagnostic delay
- Give 30% of these diagnosed children access to treatment, by doubling research avenues and projects on the mechanisms of diseases, and by doubling the number of clinical trials to ultimately double the therapeutic solutions available
- Find common denominators to treat groups of diseases by targeting common mechanisms
- Continue to enhance the Institute's exceptional cohorts, starting points for all research work and the advances of tomorrow.

Following its assessment by an international jury in June 2019 for the purpose of extending its IHU label and the meeting of its International Scientific Advisory Board in October 2019, *Imagine* keeps a high level of innovation and flourishing science at the heart of its priorities. With this in mind, *Imagine* has also set itself targets over the next few years:

- Continue its opening outwards and its scientific resurgence, particularly internationally, through the recruitment of new teams as well as international collaborative projects, and expand its horizons and fields of action towards the human and social sciences
- Invest in technological innovation, with the renewal of its platforms, the implementation of its Labs-in-Labs hosting facility, an *Imagine* platform for innovative manufacturers and companies, and the launch of Springboard, the world's first financial accelerator dedicated to genetic diseases
- Accelerate its bioinformatics, genomics and data processing programs by strengthening its resources
- Support students and young researchers with a structured teaching offer, career support and a mentoring system.

DISCOVERING

DISCOVERING HOW A DISEASE ORIGINATES IS ESSENTIAL TO UNDERSTANDING ITS MECHANISM

"Today still, more than one in two children leave genetic consultations without a diagnosis. However, without diagnosis, there is no specific treatment. Diagnosis is the mechanism behind the disorders, their signature and their reason for being. This is the 'sine qua non' for further research and, therefore, care."

Prof. Stanislas Lyonnet,
director of the *Imagine* Institute

"The diagnostic delay was for us the most difficult period in our son's illness. You wonder if you're crazy, you don't have anything to rely on. Putting a name on a disease or on the cause of the disease opens up avenues; it allows us to rely on something, to break the impasse and move towards the future."

Parents of five-year-old Louis, who has a genetic disease currently being diagnosed.

Before you can consider treating a genetic disease, you must first understand and name it. Three steps are necessary: identify the gene(s) responsible for the disorders; characterize their mutations to understand the disturbances they generate and transfer these data towards basic research and also diagnostic tools; and finally, clinical research. These steps also make it possible to provide genetic counseling to families.

"One of the great questions of modern genetics is the annotation of variants, i.e., the identification of information useful to the patient, among the mass of information accessible in his or her genome. The challenge is immense, but we believe we can do it. Today, about 50% of children who attend a genetic consultation leave without a diagnosis – but this is changing. This must and will change through cutting-edge research, an excellent clinic, increasingly powerful methods, and global collaborations. In less than ten years, we hope that 80% of these children will have a name for their illness," explains Prof. Stanislas Lyonnet, director of the *Imagine* Institute.

It is to answer this public health question, accelerate discoveries and provide answers to families affected by genetic diseases, that the joint Inserm/Université de Paris teams at the *Imagine* Institute are collaborating in a decompartmentalized, interdisciplinary and translational approach around patients.

Starting with the patient and ending with the patient, the research and care teams and reference centers affiliated with *Imagine* struggle on a daily basis. In 2019, these teams mobilized their knowledge and talents to advance research and identify new genes and mechanisms, and published 862 scientific articles in national and international journals.

The discovery of new genes is the first step towards diagnosing and understanding the disease

In 2019, **the team headed by Gaël Ménasché and Fernando Sepulveda**, which works on the molecular bases of the abnormalities of immune homeostasis, uncovered a new function of the *TTC7A* gene. By examining the role of the TTC7A protein in the production of blood cells in an animal model, they discovered that alteration of the *TTC7A* gene causes greater resistance of hematopoietic stem cells to stress and greater turnover of blood cells, resulting in a major risk for the body to develop hematological diseases. The team therefore describes ***TTC7A* as a regulator of hematopoietic stem cell self-renewal and stress response**. (*Haematologica*, December 2019).

Frédéric Rieux-Laucat's team

Mickaël Ménager's team

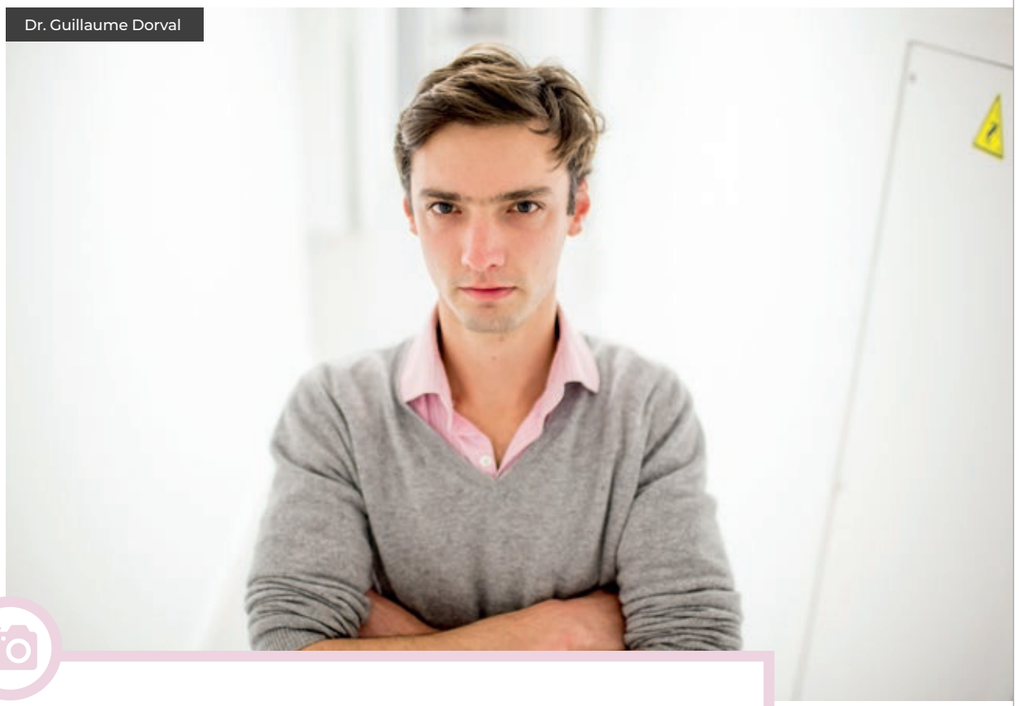
The team led by **Laurence Legeai-Mallet and Valérie Cormier-Daire**, specializing in the molecular and pathophysiological bases of osteochondrodysplasias, has reported **new genetic mutations that cause Beemer-Langer syndrome (BLS) or BLS-type**, a genetic disease characterized in particular by multiple skeletal anomalies and death *in utero* or at the start of the neonatal period following respiratory failure. This discovery reveals the possible involvement of the *IFT80* gene in ciliopathies, and its diagnostic value for BLS (*Am J of Medical Genetics*, April 2019).

Ciliopathies, defects in the formation or function of cilia, an organ present on the surface of most of our cells, had already been associated with mutations in genes coding for the components of intrafragellar transport complexes (IFTs). The team headed by **Sophie Saunier and Corinne Antignac**, while exploring mutations in one of these genes, the *IFT52* gene, has uncovered a new function for regulating microtubules, the transport rails that adorn cells, and the cohesion of centrosomes, the centers around which microtubules are organized (*Hum Mol Genet.*, August 2019).

At the same time, the team led by **Jeanne Amiel and Stanislas Lyonnet**, focused on the embryology and genetics of malformations, discovered mutations in the *PAICS* gene in children with poly-malformative syndrome, thereby demonstrating for the first time the effects of impaired purine metabolism, essential biochemical elements for DNA synthesis (*Hum Mol Genet.*, November 2019).

Research into lymphocyte activation and susceptibility to Epstein-Barr virus (EBV), conducted by **Sylvain Latour's** team, is also making progress. In 2019, Latour's team identified concomitant deficiencies in the *PIK3CD* and *TNFRSF9* genes in a disease related to CAEBV, a rare condition in which people are unable to control infection with the generally benign EBV virus. This finding suggests that these mutations cause defects in a T-immune cell signaling pathway and subsequently, an accumulation of EBV-infected T-cells, highlighting the critical role of this signaling pathway in EBV defenses. (*J Exp Med.*, December 2019).

In terms of primary immune deficiencies, **Frédéric Rieux-Laucat's** team explored avenues of **genetic predisposition to Evans syndrome**, a rare autoimmune disease that causes the immune system to attack both red blood cells, causing chronic anemia, and platelets, disrupting blood clotting. The origin of this pathology remains unknown in most cases. By exploring the genome of 80 patients with this syndrome, the team revealed a genetic origin in 65% of them. Thirty-two of these mutations were known to affect nine genes that play a role in primary immunodeficiencies. However, twenty mutations have not yet been referenced in immune system diseases (*Blood*, July 2019).


Dr. Guillaume Dorval

MEDICINE & RESEARCH: DUAL EXPERTISE DEDICATED TO DISCOVERY

Dr. Guillaume Dorval, a pediatrician, monitors children suffering from kidney disease at the Necker-Enfants malades Hospital, some of whom suffer from nephrotic syndrome, which in 10% of cases is totally resistant to immunosuppressive treatments and develops into chronic kidney failure. In order to better understand his patients' pathologies, Dr. Dorval* was keen to do a scientific thesis in the laboratory headed by Sophie Saunier and Corinne Antignac, which specializes in hereditary kidney diseases.

"In basic science, I think it is crucial to be able to benefit from a period devoted 100% to research. At Imagine, *this is common: many doctors are also researchers and vice versa,"* he said. It was this dual expertise that enabled him to discover a new gene at the origin of corticoresistant nephrotic syndrome.

Analysis of a patient's exome revealed a mutation with high pathogenicity scores in the *TBC1D8B* gene. Through a European data sharing program, another patient was identified in Bristol in the United Kingdom, with another mutation in the same gene. Functional *in vivo* and *in vitro* studies uncovered a cellular mechanism due to mutations in this gene, the alterations of which had never been described in nephrotic syndrome, thus opening the way for new discoveries. Some patients with corticoresistant nephrotic syndrome will therefore have their diagnosis clarified, and genetic advice can be offered (*Am J of Human Genetics*, February 2019).

*Dr. Guillaume Dorval benefits from the Health-Science (MD-PhD) Program funded by the Bettencourt Schueller Foundation.

Understanding mechanisms, a step towards a therapeutic solution

The team led by **Matias Simons,** specializing in epithelial biology and kidney diseases, has identified **genetic variants that could be protective for the kidneys**. Proteinuria (protein in the urine) accelerates kidney and cardiovascular diseases. However, in patients with a mutation in the cubilin gene, proteinuria does not result in any renal dysfunction or pathology. By sequencing the genome of larger patient cohorts, Matias Simons and his team showed that certain variants were even associated with better kidney function in people with chronic kidney disease. They therefore discovered that cubilin inhibition, by hindering the absorption of proteins in the proximal tubules of the nephron, could be a starting point for a new nephroprotective strategy (*J Clin Invest*, December 2019).

In terms of genetic skin diseases, the team led by **Alain Hovnanian** has identified several avenues for **treating Netherton syndrome**, a rare and serious skin disease with a high infant mortality rate. It is caused by mutations in the *SPINK5* gene which lead to deregulation of the kallikrein 5 (KLK5) proteins, which play an important role in inflammation. Identification of five potent inhibitors of these proteins could lead to a treatment (*Bioorg Med Chem Lett*, March 2019).

In parallel, the team led by **Nadine Cerf-Bensussan**, specializing in intestinal immunity, discovered a mutation in the *STAT3* gene that caused severe enterocolitis in an adult patient resistant to standard medications and biotherapies. This discovery paved the way for a new JAK1/2 inhibitor treatment, i.e., ruxolitinib (*Gastroenterology*, March 2019).


Alain Hovnanian's team

BENEFICIAL OR EVEN HEALING GENETIC MUTATIONS

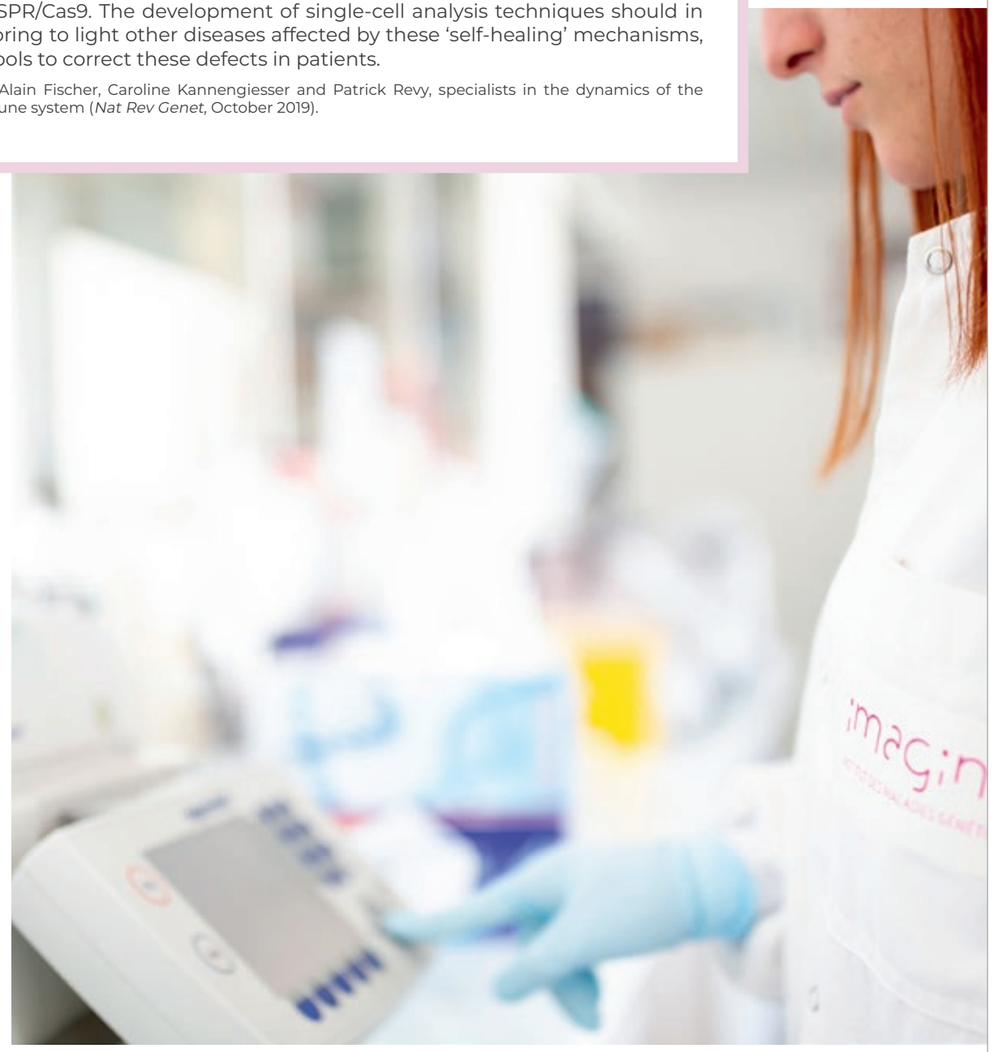
In genetics, mutation is often synonymous with disease. Damage to the DNA at the heart of our cells can result in a defective cell and thus be the starting point for genetic disease or cancer.

However, there are beneficial, even healing, mutations of very different natures: some correct the original mutation, others cause the disappearance of the DNA fragment concerned, and some indirectly restore the defective mechanism. Sometimes they result in a mosaic of healthy and defective cells, with the alleviation of symptoms in some cases.

They are mainly described in hematopoietic diseases due to germline mutations, and therefore present in all cells. Corrective mutations at the cellular level have been listed in thirty-three hereditary hematologic diseases.

These findings pave the way not only for new forms of gene therapies, but also for new therapeutic strategies based on damage repair, either *ex vivo* in T-cells, for example, or *in vivo* using CRISPR/Cas9. The development of single-cell analysis techniques should in the years ahead bring to light other diseases affected by these 'self-healing' mechanisms, along with new tools to correct these defects in patients.

Review published by Alain Fischer, Caroline Kannengiesser and Patrick Revy, specialists in the dynamics of the genome and the immune system (*Nat Rev Genet*, October 2019).



What if infectious diseases were also genetic diseases?

Prof. Jean-Laurent Casanova

Dr. Laurent Abel

Interview with Jean-Laurent Casanova and Laurent Abel, co-directors of the Laboratory of Human Genetics of Infectious Diseases at *Imagine* and The Rockefeller Institute in New York.

Why do only some people with an infectious disease go on to develop a serious disease?

J-L.C: Influenza, tuberculosis, herpes... they all start with a virus or bacterium in the body. However, while most patients recover spontaneously, others develop serious or even fatal clinical forms. During our time working together with Laurent, we have identified a hundred genetic variations, mutations and diseases that could explain susceptibility to infections.

What are the major advances in this area in 2019?

L.A: In the case of tuberculosis, we found that people who were homozygous, meaning those with two copies of a mutation in the *TYK2* gene, were more vulnerable to the bacteria causing the disease. Using a UK cohort of over 500,000 people, UK Biobank, we identified 620 people with tuberculosis. The frequency of homozygosity of the *TYK2* gene is 1% in these individuals compared with 0.2% in others. This discovery could have several consequences in terms of predictive medicine and therapy. The injection of interferon gamma could be considered in addition to anti-tuberculosis drugs. It has also been shown that homozygosity for this mutation has a protective role against certain inflammatory diseases, such as rheumatoid arthritis and Crohn's disease, leading to studies for the development of new anti-TYK2 treatments (*PNAS*, May 2019).

We have identified for the first time a genetic cause of fulminant viral hepatitis, an extremely severe form of hepatitis A that results in the destruction of the liver. Analysis of the genome of an eleven-year-old girl who died of this severe form revealed a mutation in both copies of the *IL18BP* gene, producing an altered protein, preventing her from adequately neutralizing the IL-18 cytokine. As a result, IL-18 increases the ability of immune system cells to target and destroy liver cells. This opens up therapeutic avenues for considering the administration of *IL-18 BP* to replace the defective protein (*J Exp Med.*, August 2019).

This year, we also reported a mutation in the *NLRP1* gene causing recurrent respiratory papillomatosis in two brothers. This disease is caused by human papillomavirus and results in warts growing in the throat (*PNAS*, September 2019). Finally, we found a pathway that plays a protective role during Candida infection and supports connective tissue homeostasis dependent on *TGF-beta*. In three patients in the same family who presented with chronic mucocutaneous candidiasis associated with an atypical form of connective tissue disorders, we detected Th17 immunity deficiency due to a mutation in the *MAPK8* gene (*Science Immunology,* November 2019).

What are the implications in terms of the approach to infectious diseases?

J-L. C: The impact of these advances concerns prevention, genetic counseling and the development of new therapeutic approaches in an area that remains a major cause of mortality worldwide. The acceleration of sequencing capabilities associated with bioinformatics should enable us to go even further in the study of genetic determinism to better understand infectious diseases and combat these constantly evolving pathologies.

*At the time of writing this report, Jean-Laurent Casanova and the COVID Human Genetic Effort, an international consortium, are conducting a research project to identify genetic susceptibilities that might explain the severity of COVID-19 in some patients. Jean-Laurent Casanova was also called upon to sit on the COVID Scientific Advisory Group on the advice of which the decisions of the French executive are based.

The importance of genetic testing and innovative methods for diagnosing and understanding

To be able to identify all these genetic variations, to research and understand the causes of symptoms presented by a child, to bring a patient closer to other cases, and to conduct basic, clinical and even therapeutic research projects, genetic testing and innovative diagnostic methods play a major role.

At *Imagine*, all research skills and technologies, clinical research, bioinformatics and genomics are grouped together, and 2019 was marked by new innovations in this area.

The clinical bioinformatics team led by **Antonio Rausell** developed *NCBoost*, a **new methodology** to facilitate the identification of the origin of the 4,000 genetic diseases of unknown origin identified to date. This method makes it possible to classify non-coding pathogenic variants of Mendelian diseases (*Genome biology*, December 2019).

For its part, the team led by **Mickaël Ménager**, specializing in inflammatory responses and transcriptomic networks in diseases, explores our immune system and its failures in the face of viral or bacterial attack thanks to *Big Data*, artificial intelligence and single-cell analysis technologies. In 2019, his team developed an approach combining experiments and computational biology to **map innate response** following HIV-1 infection in dendritic cells. The results of this mapping and its impacts on therapeutic diagnostic approaches will be published in 2020.

Mickaël Ménager's team

Antonio Rausell's team

INNOVATING TO CURE

BUILDING THE BEST SCIENCE TODAY FOR THE BEST MEDICINE OF TOMORROW

"Imagine confirms today that our dream at the time of its creation, namely that together, by bringing together our common expertise, we would go faster and we would do better, was realistic. At Imagine, the best science meets human and innovative medicine for the benefit of sick children."

Prof. Alain Fischer, co-founder and first director of the *Imagine* Institute

"Genetic testing began when Louis was one year old. Today, he is five, and we have an avenue to pursue, but before we were at an impasse. Now we can rely on something. We are focused on day-to-day care and Imagine continues to work to find."

Parents of five-year-old Louis, who has a genetic disease currently being diagnosed.

"The waiting phase, regardless of the tests, is long and difficult,» explains Prof. Stanislas Lyonnet, director of* Imagine. *«Genetics, because of the interpretation of tests, is a complex discipline. This will change and improve as time goes by, but for families, this time spent waiting remains a challenge during which, more often than not, there is still no referral to a healthcare system."

Diagnosis is about finding the reason for the disorders; however, diagnosis is also a signature that opens the way to genetic counseling, brings families together, and is essential for further research and the development of targeted treatments.

"Genetics necessarily involve the clinic. The more genetics there are, the more a quality clinic time is necessary," recalls Prof. Stanislas Lyonnet. *Imagine* was designed to accelerate this shift from clinic to research and *vice versa*. The discoveries being made continue to demonstrate this. In 2019, Olivier Hermine's team discovered that serotonin, a molecule produced in the bone marrow, can affect the production of blood cells, opening a new therapeutic avenue for myelodysplastic syndromes. The origin of these syndromes is related to an abnormality of progenitor cells of the red blood cell line. Patients suffering from anemia require regular transfusions and sometimes treatment with erythropoietin (EPO). Research conducted at *Imagine* suggests that correcting patients' serotonin levels, with an antidepressant, for example, could help improve their anemia.

From basic research to treatment

At *Imagine*, everything is done for the patient. *Imagine* is a true center of expertise which, in addition to housing research laboratories and cutting-edge platforms, combines twenty-five reference centers for rare diseases, six clinical Units and two clinical investigation centers (CIC) at Necker-Enfants malades Hospital. This unique continuum of research and care provides optimal care for children and their conditions.

Thus, by working together, doctors and researchers, and in many cases doctor-researchers, improve knowledge of genetic diseases, their management, and innovate in terms of treatment. These advances could not be made, and especially not deployed on a wider scale, without collaborations with industrial companies and biotechs.

AUTISM SPECTRUM DISORDERS: DISEASES THAT REMAIN POORLY UNDERSTOOD

2019 was marked by several advances made by *Imagine* medical researchers on the autism spectrum disorders (ASD) front. This major communication disorder, which affects 700,000 people in France, is one of the leading causes of consultations at Necker-Enfants malades Hospital, at *Imagine*.

Prof. Arnold Munnich, President of the *Imagine* Foundation, has shown that the genetic forms of ASD are still largely underestimated. Over a twenty-year period, a mobile team of geneticists from the *Imagine* Institute and the Élan Retrouvé Foundation reached out to 502 ASD patients and their families at twenty-six specialist institutions to offer them genetic consultations: *"The results show that combining the NGS technique with CGH* and screening for Fragile X syndrome can significantly improve the accuracy of diagnosis"*, he explains.

At the same time, the cerebral imaging laboratory headed by Prof. Nathalie Boddaert, *Image@ Imagine*, used MRI and eye tracking to find a cerebral signature of our degree of sociability. The team showed that studying eye patterns can provide objective information on social behavior. The way we look at other people is unique to each individual, and does not change over time. These results provide new insights into variability in social behavior and its neural substrates, and may also contribute to a better understanding of ASDs.

[*Editor's note: NGS, i.e., Next-Generation Sequencing, is a set of high-throughput DNA sequencing methods. CGH, i.e., Comparative Genomic Hybridization, is a technique to analyze chromosomal copy number changes in DNA].

Imagine is at the forefront of gene and cell therapies

Since its creation, *Imagine* has contributed to the development of innovative therapies, both gene and cell, to experimental research and to the clinical validation of new approaches.

In March 2019, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) issued a favorable opinion for the Marketing Authorization (MA) for Zynteglo by Bluebird Bio for patients with transfusion-dependent beta-thalassemia (TDT). Since 2013, this biotechnology company has been conducting clinical studies in collaboration with **Prof. Marina Cavazzana**, a researcher at *Imagine* and physician at Necker-Enfants malades Hospital, specializing in gene therapy for the treatment of hemoglobinopathies. Recent clinical data from the HB-205 study of four patients managed at Necker-Enfants malades Hospital revealed the therapeutic efficacy of Zynteglo in TDT patients for whom a transfusion-compatible donor was not available. More than three years after treatments, fourteen of the twenty-two patients treated no longer need blood transfusions, while others have permanently reduced their transfusion requirements.

In 2019, the Institute also strengthened its partnership with the young biotechnology company Tree Frog Therapeutics, dedicated to the production of stem cells for therapeutic purposes. Winner of the I-Lab Prize of the Ministry of Higher Education, Research and Innovation, in 2019 the start-up delivered a first batch of stem cells with high quality control to *Imagine*, to develop new therapeutic avenues in the field of cell therapies.

Prof. Marina Cavazzana

Laurence Legeai-Mallet

Continuing to develop innovative treatments

Imagine and its researchers have already demonstrated their unique abilities in uncovering new therapeutic approaches.

In 1994, **Laurence Legeai-Mallet**, long before the creation of *Imagine*, which she joined when it opened, codiscovered the gene responsible for achondroplasia, the most common form of dwarfism. Since then, she has continually explored the mechanisms deregulated by the alteration of this gene and has developed unique animal models to test various drug candidates. In 2019, a first experimental treatment, directly resulting from her research, was assessed worldwide by the company Biomarin, and was proposed as part of a clinical trial to children from the Necker-Enfants malades Hospital, who came in for a consultation on the very ground floor of the building where Laurence Legeai-Mallet and her team continue to explore new avenues. Although the results are not yet final, they seem very encouraging. This 'virtuous loop' perfectly symbolizes the *Imagine* model, which also supports scientists as they move through the different – and sometimes long and laborious – stages from discovery to clinical validation of the new approaches proposed, including pre-clinical models.

Promoting clinical trials

Once laboratories have gathered all the necessary preclinical evidence in relation to potential treatments or diagnostic methods, the next step is clinical development.

To do this, the *Imagine* Institute provides resources to clinical research teams and rolls-out clinical research programs. **Clinical research is an essential stage in the development of new diagnostic and therapeutic approaches that improve patient care.**

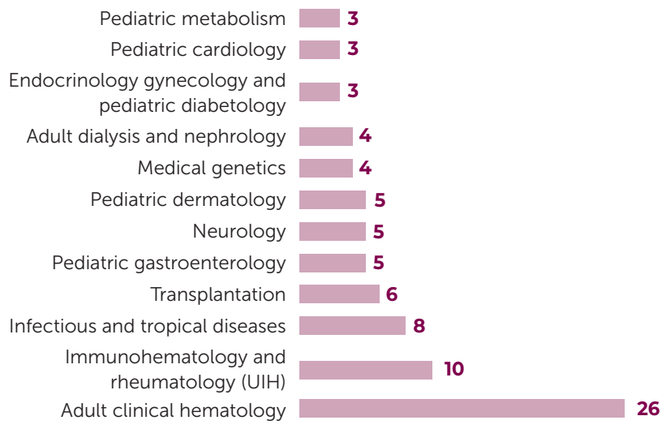
Imagine's clinical research team, led by Salma Kotti, serves the reference centers for rare diseases and clinical departments of the Necker-Enfants malades Hsopital which constitute the clinical scope of *Imagine*, in addition to the clinical research platforms at Necker-Enfants malades. The promotion team is composed of two project managers in the of the IHU 'Track' AP-HP *Imagine*, the IHU 'Track' Inserm *Imagine*, and a clinical research associate. The investigation team is composed of clinical research coordinators (CRCs), clinical trial technicians (CTTs) and mobile clinical research nurses (MCRNs).

"The transition from basic research to clinical trial is a long process; we help the researchers and clinicians of our founding members the AP-HP, Inserm and the Université de Paris throughout this process, which requires distinct expertise. First of all, the feasibility of the study must be assessed, assistance with setting up the project and drafting the protocol, carrying out regulatory submissions and then selecting patients and managing the issues that arise on a day-to-day basis," explains Salma Kotti.

In 2019, fifteen reference centers of the twenty-five affiliates benefited from *Imagine* investigation assistance in the management of their clinical trials. CTTs/CRCs and MCRNs were thus able to help set up and initiate studies, select patients and manage clinical trials on a daily basis. The investigation assistance team at *Imagine* supported 33 clinical trials in 2019, enabling the inclusion of 180 patients.

In 2019, 544 clinical studies involving over 7,500 patients were ongoing within the clinical scope of the *Imagine* IUH, including the reference centers for rare diseases, the clinical departments, and the two clinical investigation centers at Necker-Enfants malades Hospital. Of these studies, 80% were conducted by twelve clinical departments, as shown in the figure below, and more than 55% were conducted primarily by twenty investigators.

Twelve main clinical departments conducted clinical studies in 2019




Prof. Stéphane Blanche

Humanizing care management

The three mobile clinical research nurses in the clinical research team at *Imagine* play a key role in the care of patients included in clinical trials. They take the samples that are essential for the trial and act as a link between the care teams and the clinical trial sponsors.

"As part of clinical trials, we monitor patients over months or even years," explains Léa Péroni, an *Imagine* clinical research nurse. *"What is great is that we have time to explain the exams to them and answer their questions."*

Nurses jointly develop with reference centers (Intellectual Disabilities, Developmental Anomalies and Constitutional Bone Diseases, etc.) personalized care pathways for children.

In 2019, thanks to the help and generosity of the Sisley Foundation, the team was able to implement its project to renovate the *Imagine* Mobile Nurses Box. They can now perform all nursing procedures and answer parents' and children's questions about consent in a more appropriate, warm and less anxiety-inducing environment. This new bright and colorful space also makes it possible to improve how patients are welcomed, particularly those with intellectual and motor disabilities.

Reference centers for rare diseases: an innovation accelerator for the benefit of patients

When confronted with a genetic disease, the expertise of doctors who have already had to deal with such a disease, which is often rare, is crucial. The reference centers and rare diseases networks have been designed for this purpose: to organize and structure care networks in order to offer patients optimal care, wherever they are.

Beyond research, reference centers for rare diseases take into account all facets of a child, and consider them a person, not just a disease, guiding them through the transition to adulthood. Every one expresses their illness differently, and it is necessary to understand the mechanism of a disease, to take into account a person and a family as whole entities.

In support of these centers, of which 25 fall within the Institute's scope (see pages 32 and 33), the *Imagine* teams have set a target of increasing clinical trials two-fold. It is an essential step to then be able to offer new therapeutic solutions on a wider scale.

***"The reference centers for rare diseases do everything possible for the patient, their family and loved ones on a daily basis,"* explains Prof. Christine Bodemer, president of the Necker–AP-HP Rare Disease Commission-Center Université de Paris, Head of the Dermatology Department at Necker-Enfants malades Hospital and Head of the Reference Center for Genetic Diseases with cutaneous expression (MAGEC). *Because suffering is shared by us all. These centers also look to the long term and guarantee the progress of tomorrow by deploying clinical research.*"**

25 reference centers for rare diseases affiliated to *Imagine*

Hematology:

PEDIATRIC HEMOPHILIA
Annie Harroche

MASTOCYTOSIS
Olivier Hermine

MAJOR SICKLE CELL SYNDROMES
Marianne de Montalembert

Neuro-development:

INTELLECTUAL DISABILITIES OF RARE CAUSES
Marlène Rio

DI – RETT CENTER
Nadia Bahi-Buisson

RARE OPHTHALMOLOGICAL DISEASES
Dominique Brémond-Gignac

HEREDITARY METABOLIC DISEASES
Pascale de Lonlay

MITOCHONDRIAL DISEASES
Jean-Paul Bonnefont

RARE EPILEPSIES
Rima Nabbout

Immunology-Infectiology:

HEREDITARY IMMUNO-DEFICIENCIES
Alain Fischer

RARE DIGESTIVE TRACT DISEASES
Olivier Goulet

JUVENILE ARTHRITIS
Pierre Quartier dit Maire

Nephrology:

HEREDITARY KIDNEY DISEASES OF THE CHILD AND ADULT
Rémi Salomon

Development and cardiology:

PIERRE ROBIN SEQUENCE
Véronique Abadie

DEVELOPMENTAL ABNORMALITIES AND MALFORMATION SYNDROMES
Jeanne Amiel

GENETIC DISEASES WITH CUTANEOUS EXPRESSION
Christine Bodemer

COMPLEX CONGENITAL HEART DEFECTS
Damien Bonnet

CONSTITUTIONAL BONE DISEASES
Valérie Cormier-Daire

RARE ENT MALFORMATIONS
Françoise Denoyelle

GENETIC DEAFNESS
Sandrine Marlin

CRANIAL AND FACIAL MALFORMATIONS
Arnaud Picard

RARE GYNECOLOGICAL PATHOLOGIES
Michel Polak

RARE ANORECTAL AND PELVIC ANOMALIES
Sabine Sarnacki

CRANIOSYNOSTOSIS
Michel Zérah

VERTEBRAL AND SPINAL MALFORMATIONS
Michel Zérah

From discovery to innovation

Imagine, with the support of its Innovation and Valorization Department 'DIVA', has since its creation demonstrated its ability to accelerate translational and clinical research efforts, and to promote these developments to socio-economic partners. At the time of writing this report, *Imagine*, already 'Tremplin Carnot' certified since 2016, has just been certified by the 'Carnot Institute', by the Ministry of Higher Education, Research and Innovation, in recognition of the quality and dynamism of its partnership research activities within the industry. *"This Carnot Institute label is awarded for four years. It will enable us to significantly grow and fund our R&D partnership development efforts. The label also provides our partners with a guarantee that collaborative projects are examined and implemented according to best practices"*, explains Romain Marlange, director of the Innovation and Valorization Department at the *Imagine* Institute.

Protect, (co-)develop, transfer

With a view to industrial transfer, one of the first steps is to protect scientific results by all necessary means – firstly by filing a patent. **In 2019, 10 new patents were filed**. The *Imagine* patent portfolio covers a very broad spectrum of applications and includes 50 active patent families. These patents and other expertise developed at *Imagine* have already resulted in the signing of 12 operating licenses. Many developments are conducted in partnership with companies in order to more effectively ensure the industrialization and marketing stages necessary to disseminate advances for the benefit of patients. Since the creation of *Imagine*, partnership research has increased two-fold. In 2019, 30 new R&D partnership agreements (or amendments) at the preclinical stage were signed, and more than 60 new clinical studies involving industrial partners were put in place; all industrial contracts in effect in 2019 generated more than €5 million in revenue, invested in the Institute's research activities. Some projects give rise to the creation of start-ups: since 2012, 10 start-ups, including 6 resulting from *Imagine* research, have been created. The other four were propelled through the Bioentrepreneurs program, a program for training entrepreneurs and speeding up health-tech start-up projects, a real springboard to entrepreneurship and value creation in the biomedical sector.

Initiating the most innovative projects

To stimulate the most innovative projects, *Imagine* has set up two internal initiation schemes: ***Cross-Lab*** for projects that transverse several research teams (laboratories, platforms and reference centers) and from which disruptive innovations can be expected; and ***Innogrant***, for projects with high industrial transfer potential.

In 2019, 4 ***Cross-Lab*** projects launched in 2018 were still ongoing, in the fields of microcephaly, mitochondrial and autoimmune diseases, keratinocyte-leukocyte interactions and artificial intelligence in dysmorphology. A fifth project, initiated in 2017, resulted in a larger project in 2019 involving the pharmaceutical laboratory Sanofi and the company Ariana Pharma, winner of the 'University Hospital Health Research (RHU)' call for projects launched by the ANR as part of the Investments for the Future Program.

Two projects were able to benefit from the Innogrant pre-maturation scheme in 2019. Of the 6 projects funded by this scheme since 2017, one has already given rise to the creation of the start-up CoDoc, promoting the Dr. Warehouse biomedical data storage solution. Two other projects were directed towards the ***Springboard*** program, *Imagine*'s new innovation support system, which was launched in February 2020. It is the first financial and expertise accelerator dedicated to genetic diseases. Springboard is an accelerator program for upstream projects with strong potential for transfer in the therapeutic, diagnostic or care field, for the benefit of patients, primarily via the creation of start-ups.

Thus, *Imagine* deploys the expertise and all the resources necessary to support researchers in their innovation and technology transfer projects. In addition, *Imagine* is part of a very dynamic ecosystem, conducive to the development of biomedical innovations, and it contributes to developing this ecosystem.

Alessandra Pierani's team

Lab-in-labs, a hosting platform for manufacturers

Imagine hosts innovative companies operating within its fields of activity on its Lab-in-Labs platform. In 2019, Medetia Pharmaceuticals, a partner in the C'IL-LICO project and winner of the RHU3 program, joined this platform. This bringing together of researchers and physicians on the one hand, and manufacturers on the other, facilitates the emergence and development of the most ambitious partnerships.

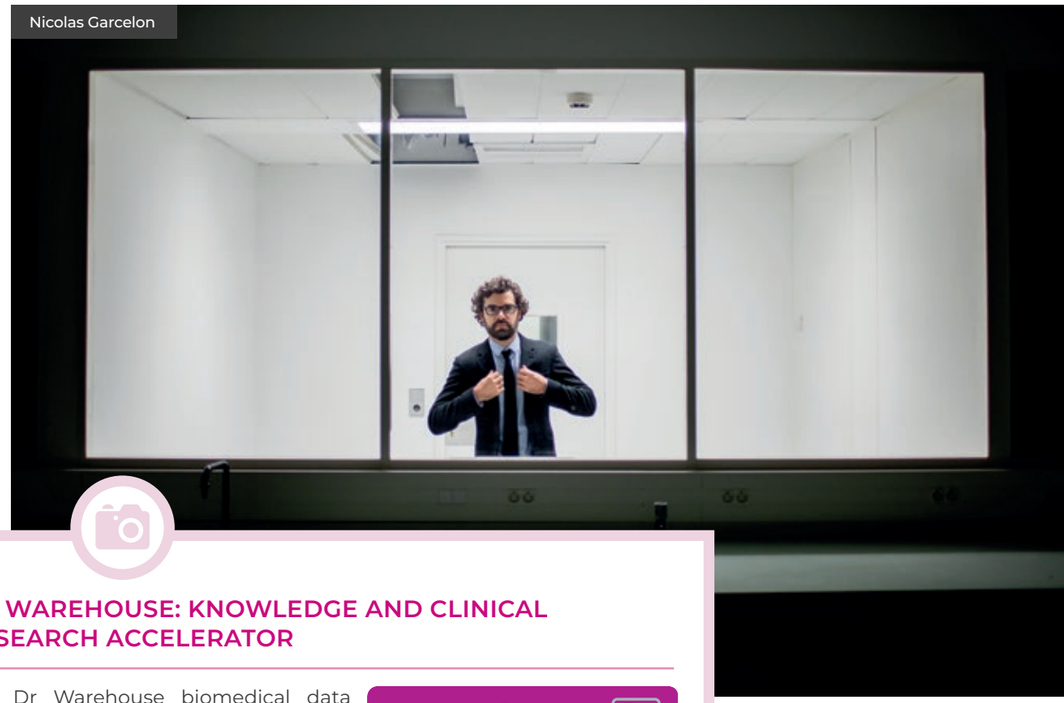
France Biotech, the French association of health innovation entrepreneurs, has also been hosted at *Imagine* since 2018. Beyond this local ecosystem, *Imagine* is a partner of the Findmed consortium, which brings together the Carnot Institutes in the field of health and chemistry, and a member of Medicen Paris Region, a global competitiveness cluster, and a privileged partner of the Human Health Start-Up Factory consortium, coordinated by Inserm Transfert.

Major projects with manufacturers

In 2019, three major research projects – one coordinated by *Imagine* and two with which *Imagine* is associated –, involving industrial partners, were selected as part of the ANR 'Hospital-University Health Research (RHU)' call for projects for the Investments for the Future Program, aimed at supporting large-scale innovative research projects in the health field. The ATRACTion project, led by **Frédéric Rieux-Laucat**, director of a laboratory at *Imagine*, focuses on primary immune deficiencies, the Institute's major areas of expertise, and brings together eleven partners, including Inserm, AP-HP, INRA, CEA, Université de Paris, Sanofi, and Ariana Pharma. *Imagine* is also involved in the IRIS projects, led by **Prof. Marina Cavazzana** and coordinated by the AP-HP in the area of gene therapy; and COSY, designed by **Prof. Guillaume Canaud** and coordinated by Inserm in the area of dysharmonious hypergrowth syndromes.

Moreover, in 2019, *Imagine* won the Sésame Filières PIA call for projects, opening up its single-cell analysis platform beyond the *Imagine* laboratories to the industrial community.

Nicolas Garcelon



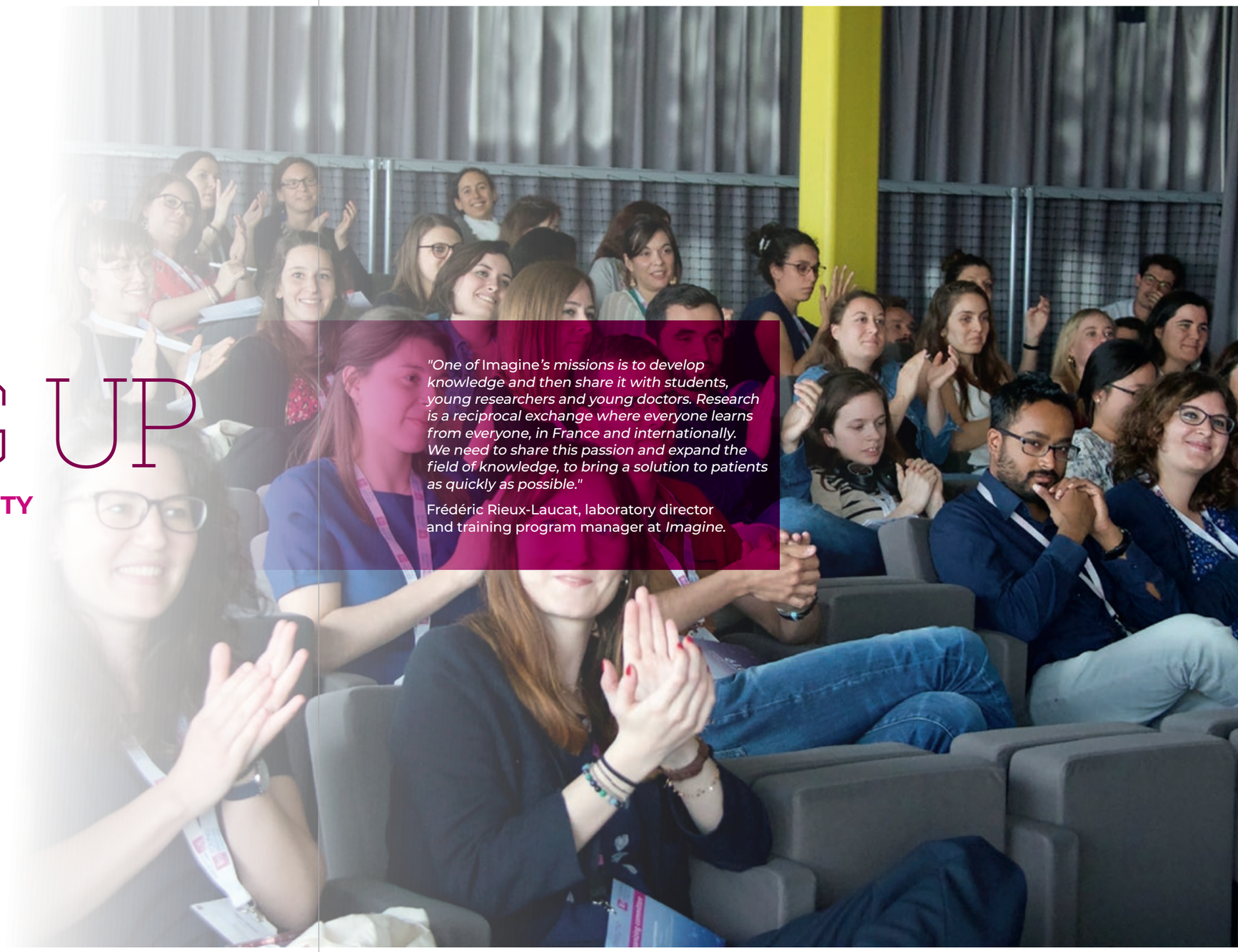
DR WAREHOUSE: KNOWLEDGE AND CLINICAL RESEARCH ACCELERATOR

The Dr Warehouse biomedical data repository was developed by the data science platform directed by **Nicolas Garcelon**.

Intended for doctors, Dr. Warehouse, with its open source database architecture, makes it possible to build cohorts for clinical trials based on textual analysis. During its use at Necker-Enfants malades Hospital, the anonymized data of more than 700,000 children have already been listed. In addition to being numerous, they are of excellent quality: medical reports, imaging, anatomical pathology analyses, and so on. Dr. Warehouse offers the possibility of reconciling previously unrelated files and thus forming patient groups for a study. It also reveals issues that had not been raised. The Codoc company was created in 2017 to offer hospitals installation, maintenance and training services relative to this solution.

OPENING UP

BEING AN ACTOR IN SOCIETY



"One of Imagine*'s missions is to develop knowledge and then share it with students, young researchers and young doctors. Research is a reciprocal exchange where everyone learns from everyone, in France and internationally. We need to share this passion and expand the field of knowledge, to bring a solution to patients as quickly as possible."*

Frédéric Rieux-Laucat, laboratory director and training program manager at *Imagine.*

"The whole family felt very alone faced with the illness that affects our son, with the lack of information, the inability to understand, to knock on the right door and to talk about it. It is essential to raise awareness and inform people about genetic diseases, to educate families, and to unite all forces around patients and their families."

Parents of five-year-old Louis, who has a genetic disease currently being diagnosed.

The purpose of *Imagine* is to transmit and disseminate knowledge, not only to the scientific and medical communities on an international scale, but also to the general public, thereby expanding research horizons.

"We wanted to put Imagine at the heart of society and in the hearts of citizens. The societal vision of Imagine is above all to bring to the public's attention honest, authentic and genuine information in the face of numerous fake news stories, for the good of families," says Prof. Arnold Munnich, president of the *Imagine* Foundation. And this will happen by training the doctors and researchers of tomorrow, and by the continuous training of doctors and healthcare professionals.

Teaching and transmission, priority missions at *Imagine*

At *Imagine*, students, researchers, physicians-researchers and bioentrepreneurs benefit from dedicated training in their commitment to excellence. These programs promote research-medicine dual expertise, which is the specificity and strength of the Institute. The Institute's doctors and researchers also teach in bachelor's and master's programs in universities and schools.

This teaching mission is conducted with Université de Paris, a founding member of *Imagine*, and its doctoral schools, and could not develop without the very generous support of the Bettencourt Schueller Foundation.

The Bettencourt Schueller Foundation has been involved in teaching and training activities in France for over thirty years and has been an honorary patron of the *Imagine* Institute since 2012. It contributes greatly to the Institute's educational mission. In addition to funding the «Liliane Bettencourt Chair of Developmental Biology» directed at *Imagine* by Matias Simons, it provides support to the Institute's seminar center, which contributes to the dissemination of knowledge through the organization of scientific conferences and discussions, and it funds half of the research and research-based training programs (MD-PhD, Protected Time, PhD International, *Bioentrepreneurs* program).

Research and research-based training

Research and research-based training is illustrated at *Imagine* through two strategic programs aimed on the one hand at attracting new talent, and developing training in line with new needs in terms of research and care on the other. These plans make it possible to develop doctoral training for French and foreign students, the involvement of hospital physicians in research, and the training of bioentrepreneurs.

In 2019, five winners were able to benefit from these programs, and thirteen students and independent auditors joined the first session of the new Bioentrepreneurs Launchpad program, initiated in 2019.

Three doctors have also benefited from the **'Health-Science MD-PhD'** program, which allows young doctors who have already obtained a Master's 2 in research to complete their training by completing a science thesis under the supervision of a researcher from a laboratory at *Imagine*. A new student who has obtained a Master's 2 in research abroad has joined the Institute as part of the 'PhD International' program. Another doctor was the winner of the **'Protected Time for Research'** program, which aims to bring clinicians closer to the clinical or basic research developed at *Imagine* by giving them a protected time period to carry out their research project.

What they say

"Thanks to the MD-PhD program, I was able to start my science thesis at the end of my residency. It allowed me to develop my project using the Institute's many research and technological resources, while working closely with cardiopediatricians at Necker-Enfants malades Hospital."

Ségolène Bernheim, 2018 winner.

"I enjoyed the working environment and close collaboration between researchers and clinicians offered by Imagine. *I found the level of work, research and professionalism to be very high in France, with excellent research centers, and I can see myself returning to continue my scientific career there."*

Anna-Lena Neehus, 2019 winner of the PhD International program.

Training bioentrepreneurs

In 2019, *Imagine* launched the ***Bioentrepreneurs Launchpad*** program following a pilot program in 2016. *"This updated program follows on from the Master Bioentrepreneurs that we launched at Imagine with prestigious partnerships (X and HEC), which aims to give young students from our universities a lively training course in the field of entrepreneurship in biotechnology, with real subjects, drawn from the work of the Institute's researchers"* recalls Stanislas Lyonnet, director of *Imagine*. This program for training entrepreneurs and accelerating healthtech start-up projects, with a strong impact for patients, is a genuine springboard to entrepreneurship and value creation in the biomedical sector. It is aimed at science students, doctors, pharmacists, engineers and managers. Led by Prof. Olivier Hermine, it takes place in two phases: the first brings together students, doctors and researchers who are proposing projects (see below); the second takes the form of a nine to twelve-week *bootcamp*, wherein the teams work full-time on their projects. The program is also open to independent auditors. It is recognized by the Master's 2 AIRE (Université de Paris) and by the MSc X-HEC Entrepreneurs (Ecole Polytechnique and HEC Paris). The Université de Paris, HEC Paris and the Ecole Polytechnique are still partners.

THE LAUNCHPAD BIOENTREPRENEURS 'MATCHING DAY'

On October 14, 2019, academic researchers and practitioners, and student entrepreneurs, met at *Imagine* on the occasion of 'Matching day'. This event brought together project leaders, students, alumni, partners and stakeholders from the *Imagine* Bioentrepreneurs Launchpad program, and structures for promoting the projects proposed around presentations, round tables and discussions. Projects from the *Imagine* Institute, other Carnot Institutes, and the AP-HP. Centre–Université de Paris were presented to students of the partner masters programs of the 'Bioentrepreneurs' program (MSc, X-HEC Entrepreneurs, M2 AIRE Track Bioentrepreneurs of the Université de Paris). This event launched the team building phase around the projects.

Training future generations

Nearly a third (31%) of the members of the *Imagine* Institute are students, doctoral students or postdoctoral fellows. Training these students, future doctors, and researchers is a priority. In addition to training programs, *Imagine* offers a rich institute way of life, and allows students and young researchers to benefit from events and synergies between the institute members.

The *Imagine* Young Researchers Association (YR2I) and the *Imagine* Sport Association (ISA) organize scientific, social and sporting events throughout the year to forge relationships and promote discussion.

"YR2I supports young researchers throughout their career at Imagine *by helping them to integrate into the Institute and the scientific community. Our social events, open to all* Imagine *members, such as the Afterworks or the Olympiads, make it possible to forge real links between us. Furthermore, we also support them in developing their expertise and career vision. In 2019, they benefited from: nine seminars wherein PhD students can train to present their work; five professional breakfasts; training for PhD competitions; the invitation of international speakers; and our annual Congress. Also in 2019, we created a new event, the YUMP (Young Researchers Union Meeting in Paris) to develop the network of inter-institute doctoral students,"* explains Cyril Longé, president of the YR2I Association, created six years ago and which brings together over a hundred students, doctoral students, post-doctoral fellows, engineers and technicians.

In addition, a café for post-doctoral students was created in 2019 at *Imagine* with the aim of facilitating meetings and discussion, providing training sessions on funding methods dedicated to post-doctoral fellows, and advising them to apply to research organizations. This, notably, is in line with the recommendations of the *Imagine International Scientific Advisory Board* i.e., pay particular attention to this category of researchers.

5th CONGRESS OF YOUNG RESEARCHERS AT THE *IMAGINE* INSTITUTE

On May 23, 2019, the YR2I Association organized its fifth annual congress.

Students and young researchers presented their projects and held discussions with scientists and suppliers. The 180 participants also had the chance to attend the exceptional presentation by Dr. Philippe Charlier, from the Research and Teaching Department of the Musée du Quai Branly–Jacques Chirac, as well as see presentations by BD Biosciences and Bio Techne.

Congress of *Imagine* Young Researchers

Recruiting and training the best talent means accompanying them throughout their career, supporting their career path from the word go. Scholarships and funding were created to help doctoral students complete or continue their scientific project. Thus, funding of a few months, known as the '4th year of thesis', is granted to complete and support the thesis. Five students benefited from it through 2019 to 2020. In 2019, a thesis prize, the *Imagine Thesis Award*, was created to enable doctoral students who have defended their thesis within the three-year limit, and whose work has been published or is in the process of being published, to continue their work for six to twelve months and thus finalize their research and apply for a postdoctoral position. In 2019, two doctoral students, Meriem Belabed and Gaspard Kerner, were the winners.

The *Imagine* Young Researchers Association (YR2I)

Raising awareness among young people

For the past six years, *Imagine* has participated in the Research Apprentices Program, directed by Frédéric Rieux-Laucat and Aude Magerus-Châtinet, in partnership with the association Arbre des Connaissances. Throughout the school year, six pairs of third- and first-year students learned about professions in research and worked on a scientific project that they presented at the Research Apprentices Congress on May 22, 2019, at Institut Pasteur. The program is supported by the Bettencourt Schueller Foundation.

In 2019, *Imagine* welcomed more than forty-five placement students from high schools in Paris and the wider Ile-de-France region.

An Institute involved in its environment – and beyond

Offer scientific and medical emulation

The many areas of expertise gathered at the *Imagine* Institute and on campus at the Necker-Enfants malades Hospital result in numerous and fast-paced discussions. This means faster research and treatment development for the benefit of families affected by genetic diseases.

In 2019, at its seminar center, *Imagine* was able to organize or host 35 conferences, scientific discussions and symposia. These seminars offered researchers from the Institute's laboratories and the campus, as well as invited researchers from France or abroad, the opportunity to stay informed of their respective advances and to enrich each other to accelerate discoveries and the application thereof.

This emulation and closeness between teams, researchers and clinicians has enabled transverse and collaborative projects to take shape. In 2019, five projects selected for internal Cross-Lab funding were ongoing, one project was designated a University-Hospital Research project (RHU), and *Imagine* partnered with two further RHUs (see pages 35 and 37).

Imagine researchers are working on numerous projects involving internal and external scientists, such as the DEVO-DECODE project and DIM Gene Therapy.

Research Apprentices Congress

Continue to open up to the medical community and patient associations

The *Imagine* Institute strives to integrate as much as possible into the Necker-Enfants malades Hospital campus, and to be involved beyond the scope of its research with the medical community and patient associations.

Thus, *Imagine* has continued and even strengthened its involvement in regional or national plans and projects relating to rare and/or genetic diseases. The Institute participated in the steering and implementation of the French Initiative for Genomic Medicine 2025 through the co-steering of 'SeqOIA', the very high throughput genomics platform of the Paris region, led by AP-HP, Institut Curie, Gustave Roussy and *Imagine*, and the co-steering of the DEFIDIAG project involving geneticists, epidemiologists, economists, sociologists and psychologists to study the efficiency of the use of whole genome sequencing for the etiological diagnosis of intellectual disability. In 2019, *Imagine* was also invited to the French national steering committee of the Rare Diseases Network, and has continued to contribute to the National Plan for Rare Diseases 2018–2022. The Institute is also a partner of the EJP RD (European Joint Program on Rare Diseases) through its steering committee and through the setting up of a workshop for the 'organizing and maximizing rare disease biological sample data in biobanks.' *Imagine* also partnered with PRAIRIE (PaRis Artificial Intelligence Research InstitutE), 3IA certified (Interdisciplinary Institute of Artificial Intelligence), in 2019. At present, they are working on the ethics and human guarantee of artificial intelligence.

Second edition of the Eurordis Winterschool at Imagine

At the same time, with the idea of contributing to sharing and enriching knowledge, *Imagine* has hosted events throughout the year organized by rare disease centers and networks, on campus and across the region, as well events by patient associations. In 2019, for example, it hosted: the Pierre Royer Genetics Seminars; the Rare Diseases in Hematology and Internal Medicine Day, hosted by Prof. Olivier Hermine; the Annual Sensgene Network Day; the Reference Center on Genetic Hearing Loss Day; and the World ORKID Network Cystinosis Day.

From March 11 to 15, 2019, *Imagine* hosted the second edition of the Eurordis Winterschool, organized by Eurordis and the AnDDI-Rares network. A week of discussions and training bringing together 40 participants representing patient associations to bring the latest expertise and knowledge to patients and their families.

IMAGINE SUPPORTS THE FIRST EUROPEAN MEETING OF THE KCNB1 FRANCE ASSOCIATION

The First European Meeting of the KCNB1 France Association, supported by *Imagine*, was held on March 30, 2019, at Necker-Enfants malades Hospital. Organized by the KCNB1 France Association and Prof. Rima Nabbout, coordinator of the French National Reference Center for Rare Epilepsies, the event brought together 25 families of patients affected by a mutation in the *KCNB1* gene, from all over Europe, to discuss epileptic encephalopathy and review the research.

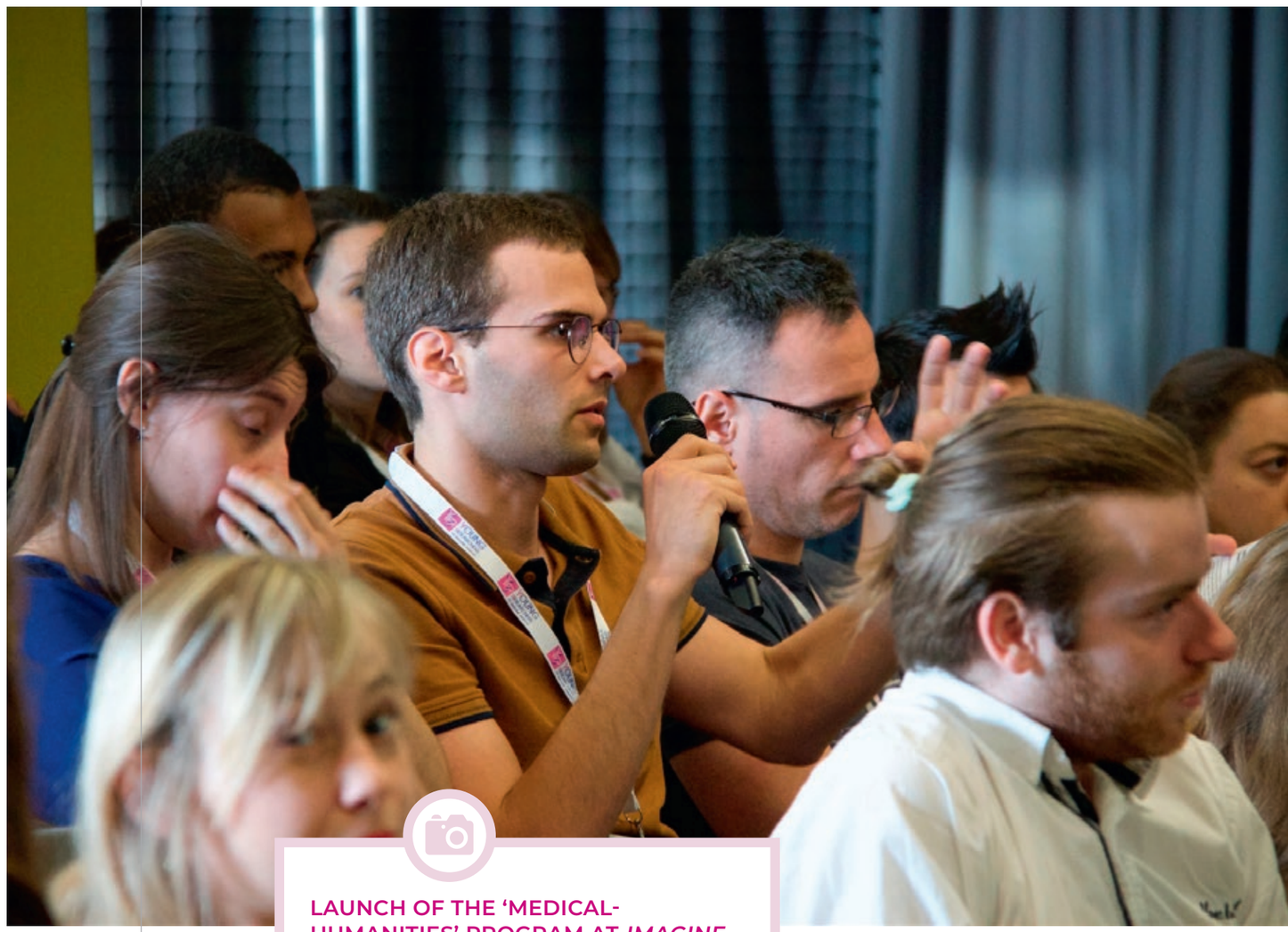
"We have come together because we are already thinking about tomorrow. If the research program leads to a therapeutic avenue, a clinical trial must be launched. By uniting with European families, we will have an even greater strike force to put it together. The more numerous we are, the more we will mobilize," explains Mélissa Cassard, president of the Association and mother to Maia, who has a genetic disease caused by a mutation in the *KNCB1* gene.

Expand horizons into the human and social sciences

A vast public health issue, genetic diseases have repercussions far beyond the scientific and medical aspects: the disease affects the entire family. Commonly associated with multiple disabilities, these often rare diseases open up a whole field of questions about the place of sick people in our societies, as well as the means to be implemented to both live with the disease and together, with the family, and well beyond.

This field of investigation is also part of *Imagine*'s missions. In 2019, it developed several programs, including one on health economics with Hospinnomics (AP-HP and PSE-Paris School of Economics) relating in particular to delayed diagnosis and access to innovation, and a program with EnsAD (French National Higher School of Decorative Arts) to develop research in adapted design. An initiative with Ethik-IA for the positive regulation of artificial intelligence in health (Sciences Po Paris Healthcare Chair, Université de Paris Law-Health Institute) was also conducted, and a seminar with the 'Hospital Philosophy Chair' was organized at *Imagine* as part of the 'Medical-Humanities' program (see opposite). In 2019, *Imagine* launched a call for projects funded by the Institute and aimed at improving the quality of life of patients, from which three winners were selected in 2020. *"Accompanying families affected by disease is one of the Institute's missions,"* explains Laure Boquet, co-manager of this program with Dr. Sandrine Marlin at *Imagine*. *"The aim of this program is to improve the life course of patients, their families and their loved ones, from diagnosis to treatment and follow-up; and to reflect on the consequences of the disease."*

Meeting with EnsAD students



LAUNCH OF THE 'MEDICAL-HUMANITIES' PROGRAM AT *IMAGINE*

Imagine is a partner of this humanities and social sciences program, supported by École Normale Supérieure, Université de Paris and AP-HP, and funded with the generous support of the Bettencourt Schueller Foundation.

On May 27, 8 students presented their work at a first seminar organized at *Imagine* in connection with the 'Philosophy Chair at the Hospital' and the 'Care: the person in medicine' (ENS) seminar on the theme: 'Birth: from conception to early childhood. Between the medical approach and humanities perspectives.» This seminar provided original and complementary points of view to the scientific approach.

In addition to developing these dedicated programs, *Imagine* took part in numerous discussions and events throughout the year on social, ethical and innovation themes. Prof. Arnold Munnich, president of the *Imagine* Foundation, spoke at a conference on genetics and human rights, organized at *Imagine*. Nicolas Garcelon presented the Dr. Warehouse software, developed at *Imagine* by the Data Science platform, at the Rare Diseases Foundation's Rare Diseases Symposium during the round table 'E-health: which opportunities for rare diseases?' Finally, Laure Boquet, general delegate of the *Imagine* Institute, took part in the 'Paris: European Capital of Health Innovation' meeting.

Raise awareness among the general public


European Heritage Days: *Imagine* guided tour

European Heritage Days: conference by Prof. Alain Fischer

Information and dialog with the general public are essential for the *Imagine* Institute to make its activities, advances and projects known, and to raise awareness about genetic diseases. To this end, the Institute has opened its doors and organized conferences.

Imagine went into action on Thursday, February 28, on International Rare Disease Day. In partnership with the Rare Disease-Chronic Disease Platform at Necker-Enfants malades Hospital, the Institute offered campus professionals and families the opportunity to take part in laboratory visits, to try careers 'speed-dating', as well as participate in workshops wherein their own DNA was extracted.

On September 21, for the European Heritage Days, the Institute opened its doors. Over 250 adults, young people and children discovered the world of genetics through a varied program: exhibitions, discovery tours, guided tours of the Institute, a DNA extraction workshop, and observation of cells under the microscope. Visitors were also enthralled by the thematic conferences hosted by researchers from *Imagine*.

IMAGINE RAISES AWARENESS IN YOUNG PEOPLE ABOUT GENE *THERAPY*

On November 6, some 150 people, most of them young people and students, participated in the *Imagine* event 'Gene Therapy: When DNA Becomes Medicine.' This round table was a great success. Organized by DIM Gene Therapy, coordinated within *Imagine* by Prof. Marina Cavazzana and supported by the Ile-de-France region, it aimed to raise awareness of gene therapy among the general public and future researchers and doctors. Around a conference-debate setup hosted by journalist Oumy Sonko and Prof. Marina Cavazzana, the participants (Valérie Pécresse, president of the Ile-de-France Regional Council; Prof. Jean-François Delfraissy, president of the National Ethics Advisory Committee; Prof. Arnold Munnich, president of the *Imagine* Foundation; Prof. Olivier Hermine, physician and director of an *Imagine* Laboratory; Prof. Christine Petit, unit director at Institut Pasteur; and Agnès Rotig, director of an *Imagine* Laboratory) explained what gene therapy is, how it works, what diseases it can cure, and what repercussions it can have.


Gene Therapy Roundtable

Collaborate internationally to progress faster

"Research cannot progress quickly without international collaboration at the highest level. We need to compare our data via informal exchanges as well as via international databases; they make it possible to compare clinical signs and genetic variants identified in patients, reconcile dossiers, or even contact these patients and ask new questions. This collaboration is not only desirable, it is above all constitutive, inherent in research on genetic diseases, and now often computerized," explains Prof. Stanislas Lyonnet, Director of the *Imagine* Institute.

Involvement at the international level begins with the attractiveness of the *Imagine* Institute and its ability to pull-in the best talent from all over the world. In 2019, 20% of the members of the Institute were foreign nationals, from thirty-seven countries in Europe and around the world.

Collaborating also means establishing collaboration or teaching agreements with institutions and teams in other countries, creating bridges on major research themes, getting involved in projects outside the Institute, and sharing knowledge at major international conferences. All the Institute's research teams collaborate with teams around the world to advance knowledge about genetic diseases more quickly.

From an institutional point of view, on March 28, during the official visit of Prime Minister Édouard Philippe, the director of the Institute signed an MOU (Memorandum of Understanding) with the Hamad Bin Khalifa University of Doha in Qatar in relation to hosting doctoral students, student exchanges and scientific collaborations. *Imagine* has also signed a collaboration agreement with the Guangzhou Women and Children Medical Center in China. Since then, the Institute has welcomed four doctoral and post-doctoral candidates into its laboratories, shortlisted by the Chinese Academy of Medicine and the University of Doha. In 2019, researcher Mickaël Ménager, laboratory director at *Imagine*, visited Japan with the aim of establishing scientific bridges and collaborations on the theme of pediatric cancers. The Institute is gradually expanding to other countries. Matias Simons, laboratory director, is leaving the Institute to move to the University of Heidelberg in Germany, where he intends to spread the *Imagine* spirit and plans to continue his fruitful collaborations with the Institute's physicians and researchers. This hiving-off of young teams thus ensures the dissemination of this *Imagine* spirit, based on bringing science and medicine together.

In 2019, physicians and researchers were very present on the international scene. For example, Prof. Corinne Antignac, laboratory director at *Imagine*, served on the scientific advisory board of the Cystinosis Research Foundation Day of Hope held from March 28 to 30, and was invited to speak at the Robert Berliner Lectures at Yale University. On May 3, Antonio Rausell, also laboratory director, was present at the Rare Disease Seminar at Yale University to present his work on non-coding DNA variants. In June, many doctors and researchers attended or spoke at the European Congress of Genetics in Sweden and the annual ASH-Hematology Congress in Orlando, USA, in December. In October, the teams of Antonio Rausell, Laurence Legeai-Mallet, and Valérie Cormier-Daire presented work on the treatment of achondroplasia at the Annual Genetics Society Congress in Houston, USA. Lastly, in November, *Imagine* hosted the very first France-UK International Conference on Ciliopathies.

This international dynamism has made it possible to obtain European grants and funding, as well as to implement collaborative projects at the European and international levels. In 2019, the European Research Council awarded prestigious funding, the ERC Consolidator Grant, to two *Imagine* team leaders: Annarita Miccio, director of the Laboratory of Chromatin and Gene Regulation During Development, for her project on innovative therapeutic strategies for beta hemoglobinopathies; and Matias Simons, director of the Laboratory of Biology and Epithelial Diseases, for the exploration of targeting tubular reabsorption as a renal protection strategy. This year, the Institute has been involved in major European projects such as: HDM-FUN on invasive fungal infections; BIND, to improve knowledge on Duchenne and Becker muscular dystrophy; and in two European training networks, SCils on ciliary signaling during normal and pathological development, and NEUcrest on the neural crest.

SOCIAL REPORT

UMR 1163 and the *Imagine* Foundation

The figures in this social report concern all staff working in the *Imagine* building.


Edor Kabashi's team

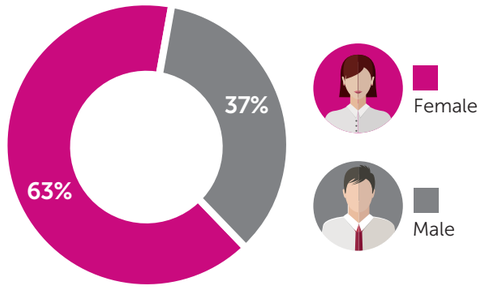
WORKFORCE

On 12/31/2019

537 PERSONS

472,07 FULL-TIME EQUIVALENT (FTE)

Breakdown of employees by gender on 12/31/2019



AFRICA

ALGERIA : **8** - BENIN : **1** - CAMEROON : **1**
MADAGASCAR : **1** - TUNISIA : **3**

AMERICA

ARGENTINA : **3** - BRAZIL : **6** - CANADA : **3** - CHILE : **2**
COLOMBIA : **3** - COSTA RICA : **1** - MEXICO : **1**

ASIA

INDIA : **4** - IRAN : **2** - JAPAN : **1** - LEBANON : **1**
TURKEY : **1** - VIETMAN : **1**

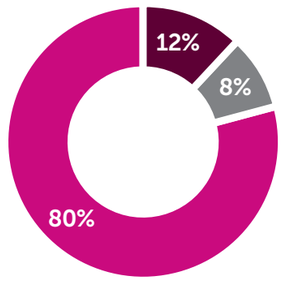
EUROPE

GERMANY : **5** - ENGLAND : **2** - BELGIUM : **2**
BULGARIA : **2** CROATIA : **1** - DENMARK **1**
SPAIN : **8** - FRANCE : **432** - GREECE : **4**
IRELAND : **1** - ITALY : **24** - LITHUANIA : **1**
POLAND : **2** - PORTUGAL : **3** - ROMANIA : **2** RUSSIA : **1**
SWITZERLAND : **1** - CZECH REPUBLIC : **1**

OCEANIA

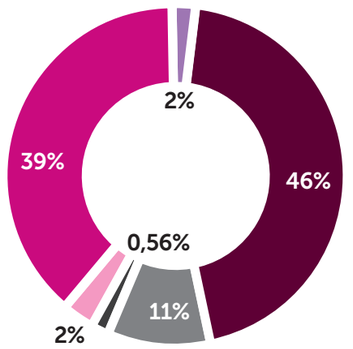
AUSTRALIA : **1**

37 NATIONALITIES

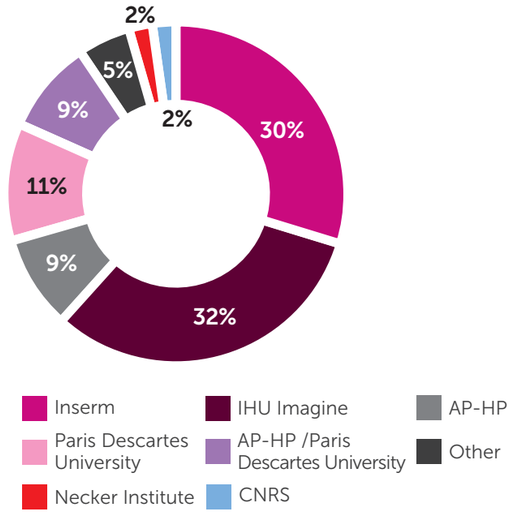


EMPLOYMENT

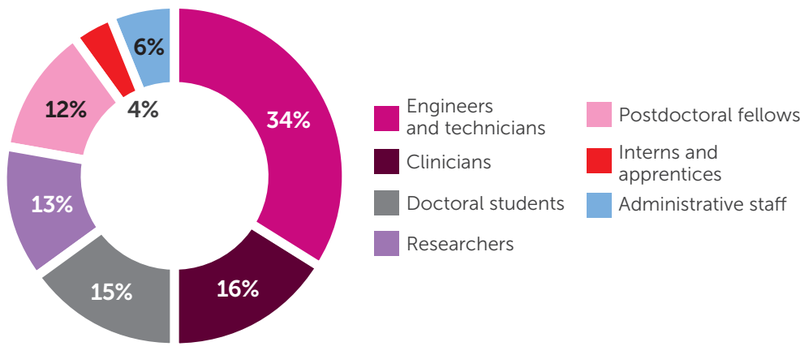
Breakdown of staff by type of contract on 12/31/2019



Breakdown of staff by employer won 12/31/2019



Breakdown of staff by occupation on 12/31/2019



Imagine Foundation

These figures only include staff employed by the *Imagine* Scientific Cooperation Foundation *stricto sensu*.

WORKFORCE

Workforce on 12/31/2019

165* EMPLOYEES ON 12/31/2019 — **162,52*** FULL-TIME EQUIVALENTS (FTE) ON 12/31/2019 — **152,75*** AVERAGE NO. OF EMPLOYEES IN 2019

142,87* AVERAGE NO. OF FTE IN 2019 — **14,9** EXTERNAL STAFF FTE ON 12/31/2019 — **8** APPRENTICES ON 12/31/2019 — **5** PROVISION

Excluding apprentices and interns

105 new contracts in 2019

5 PERMANENT

1 FIXED-TERM CONTRACT > PERMANENT CONTRACT

53 FIXED-TERM CONTRACT

20 DEFINED-TERM FIXED-TERM CONTRACT

5 CUSTOMARY FIXED TERM CONTRACT

6 APPRENTICESHIP CONTRACTS

15 PAID PLACEMENTS

74 contract terminations in 2019

44 END OF FIXED-TERM & DEFINED-TERM FIXED TERM CONTRACTS

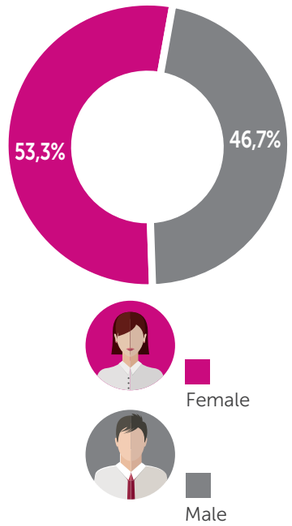
3 EARLY TERMINATION OF FIXED-TERM CONTRACTS

6 RESIGNATIONS

16 END OF PLACEMENT

5 TERMINATION OF APPRENTICESHIP CONTRACT

Breakdown of employees by gender on 12/31/2019



Employees nationalities on 12/31/2019

AFRICA

ALGERIA : **6** - BENIN : **1** - CAMEROON : **1**
MADAGASCAR : **1** - TUNISIA : **3**

AMERICA

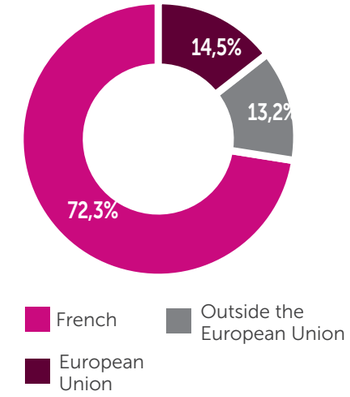
ARGENTINA : **1** - BRAZIL : **1** - CHILE : **1**
COLOMBIA : **1** - COSTA RICA : **1** - MEXICO : **1**

ASIA

IRAN : **1** - LEBANON : **1** - PHILIPPINES : **1**

EUROPE

GERMANY : **2** - CROATIA : **1** - SPAIN : **3**
FRANCE : **120** - ITALY : **12** - POLAND : **1**
PORTUGAL : **2** - ROMANIA : **1** - RUSSIA : **1**
SWITZERLAND : **1** - CZECH REPUBLIC : **1**

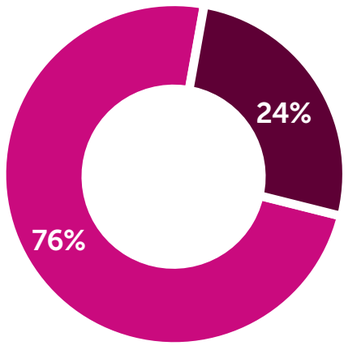


Average age of employees on 12/31/2019

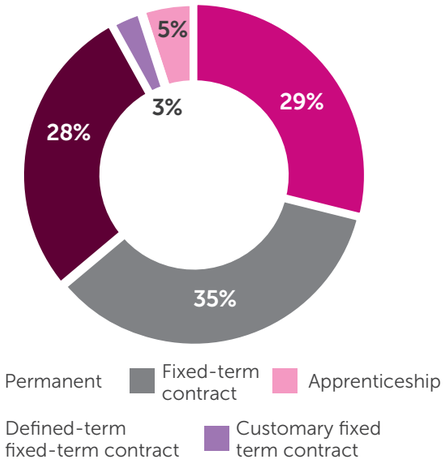
33,3 — **33,5** — **33,4**

EMPLOYMENT

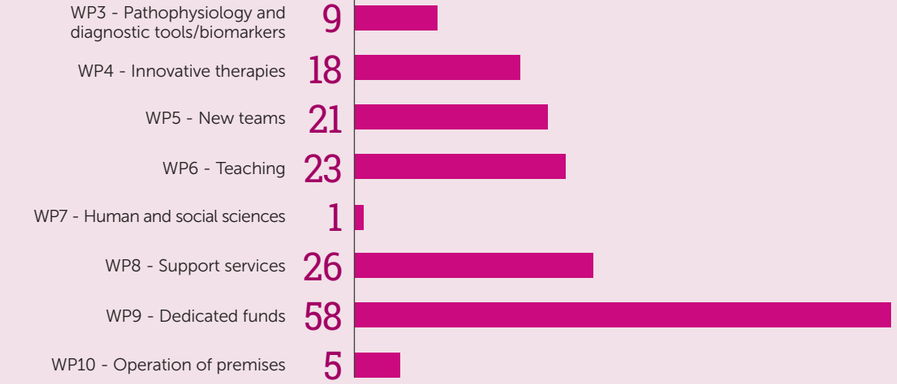
Breakdown of employees by status on 12/31/2019



Breakdown of employees by contract on 12/31/2019



Breakdown of employees by work-package (IHU program) on 12/31/2019

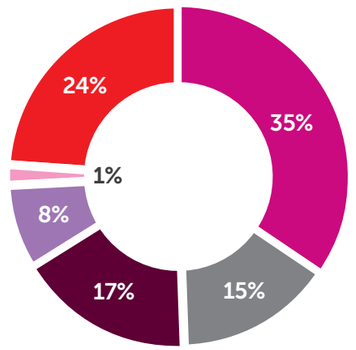


Gender equality indicator F-M*

83/100

* Based on 4 indicators: pay gap, pay-rise rate gap, % salary increase for employees in the year following their return from maternity leave, number of employees of the under-represented sex (men) among the 10 highest paid positions.

Breakdown of employees by occupational category on 12/31/2019



INTERNS

Number of interns in 2019:

INTERNSHIPS LASTING MORE THAN ONE MONTH (FROM BACHELOR'S TO MASTER'S 2): 15 (1593 DAYS)

INTERNSHIPS OF LESS THAN ONE MONTH (3RD TO MASTER'S 1): 61 (408 DAYS)

MAKING A COMMITMENT

WORKING ALONGSIDE DOCTORS AND RESEARCHERS

"It is you, through your gifts, your generous gestures and your support, that multiply the Imagine Institute's possibilities, giving it the agility and flexibility to do more and to do it faster for children suffering from genetic diseases. Thank you!"

Prof. Arnold Munnich, president of the *Imagine* Foundation

> "*My outlook on the medical profession has changed. In my mind, they were knowledgeable. And yet, when it comes to genetics, they are researchers. And it has become a team research project: the doctor does his or her job as a researcher but relies on the intimate knowledge parents have of their child. It helps foster trust in the medical profession.*"
>
> Mother of Giulia, born with multiple disabilities, carrier of an unidentified genetic disease.

***"The generosity that surrounds Imagine obliges us. It is part of a real culture of reciprocal commitment between donors and researchers. Because it is in the excellence and shared demands of these two worlds that the roots of a 'virtuous loop' of philanthropy are found, which is respectful and benevolent,"* recalls Prof. Stanislas Lyonnet, director of the *Imagine* Institute.**

The world of research is changing fast: new technologies are appearing regularly and advances are being made all over the world. We need to integrate them, take them into account, and be able to adapt and react quickly. To this end, the combination between private and public, which founded *Imagine*, is an asset. This synergy of funding from the public authorities, founding members, and sponsors, gives the Institute both the independence and responsiveness necessary to be at the forefront in the field of genetic diseases.

As a Scientific Cooperation Foundation, the *Imagine* Institute is authorized to receive donations, bequests and gifts. **This support from its loyal and precious donors and patrons is an essential lever for accelerating research and represents hope for the three million people in France affected by genetic diseases**, as Anne Meniel, who has supported the Institute for several years, reminds us: *"In a troubled and disordered world, only medical research can give us real hope. The results can be seen at* Imagine, *and help improve the living conditions of a large number of young patients with genetic diseases."*

A golden sponsor

In 2019, Teddy Riner, double Olympic judo champion and sponsor of the Institute since 2012, once again showed his full support for children. A member of the *Imagine* family, in January he attended the company party to celebrate five years since the inauguration of the *Imagine* building, and to support all staff working to advance research and care.

As a standard-bearer for car manufacturer Ford's 'Gold Test Drive' campaign, he also wanted to make *Imagine* the beneficiary of this event. From April 1 to 30, 2019, Ford donated two euros for each test drive of the new Ford Focus Active, and the Institute was also visible in advertisings campaigns – on the radio, television and at dealerships.

At the end of the year, Teddy Riner lent his voice and image to an awareness campaign at the *Imagine* Institute, with a slogan that lived up to his persona.

"Every day, researchers, physicians, patients and their families combat over 6,000 genetic diseases at the* Imagine *Institute.
So, help them, and help us, by making a donation at Institutimagine.org"

Teddy Riner at the *Imagine* launch birthday party

KIDS DO JUDO WITH TEDDY RINER

At the end of October 2019, Teddy Riner offered *Imagine* staff members' children and grandchildren, as well as sick children, eight places to participate in his judo academy.

For 3 days, the children, who were thrilled, had the opportunity to practice judo and chat with their champion, to receive his advice and techniques, and to square up against him and his coaches. A moment of happiness for these budding judokas!

"Our daughter had an incredible time; she met some great people and got a good workout. We are very grateful to Teddy, with whom she went head to head to ask questions. An unforgettable experience!" said the mother of a young patient who took part in the event.


Teddy Riner with children

Everyone is involved in promoting *Imagine*

Many of you support the *Imagine* Institute. Donors, volunteers, patrons, loyal friends, whatever form your support takes, this presence at our side strengthens the determination of physicians and researchers. Thanks to your generosity, research laboratories are constantly pushing the boundaries of knowledge about genetic diseases with the aim of discovering new treatments. Through your donations and generous actions, **you are an essential part of this collective effort.**

In 2019, 22 collections were launched on Facebook for *Imagine*: instead of a traditional birthday or wedding gift, you ask your friends to support a cause that is close to your heart, in this case the *Imagine* Institute.

Many patient associations and families were also mobilized throughout the year to make the Institute known to their friends and family and the press. Every one of your actions is a key contribution to the Institute, and every time you mobilize it strengthens the reputation of *Imagine*.

"Since the death of our child, Titouan, from a viral infection at the age of one year, my husband and I wanted to do something to prevent other families from experiencing what we have experienced. This is why we decided to donate to Imagine,» explains Fabienne, Titouan's mother. For the whole family, «giving – each in their own way – to Imagine *means helping researchers find new diagnostic methods and innovative therapeutic strategies to treat genetic diseases and thus give hope to sick children and their families."* Hence, Titouan's two sisters and their handball club, the Entente des Abers, wear a jersey every week bearing the Institute's logo.

Uniting in the face of disease

Maïa, who is now ten and a half years old, carries an extremely rare *KCNB1* gene mutation, diagnosed at the *Imagine* Institute in 2016. Her parents created an association to bring together families affected by this disease and organized the first European meetings on March 30, 2019. The KCNB1 France Association also mobilized many runners during the Heroes Race in Paris on June 23, with the In Fine Group and the support of BNP Paribas, thereby raising over €14,000.

KCNB1, In Fine Group and BNP Paribas support *Imagine* in the Heroes Race

For the second year in a row, Esprit Large's navigator, Corentin Douguet, carried the colors of *Imagine* for the Solitaire URGO Le Figaro yacht race from May 27 to June 30, 2019. *"I discovered the* Imagine *Institute with Christian Ponthieu, my co-skipper, in several Figaro races, including the Transat AC2R last year. His niece, Héloïse, suffers from a rare genetic disease and is being monitored by the Institute. When her parents asked me if we could showcase the Institute on the boat, I obviously accepted,"* he explains. He finished fourth in what is known as the toughest single-handed race.

The sporting association at *Imagine*, the *Imagine* Sport Association, has not been outdone, as it has participated in several races including the Paris Half Marathon and Paris-Versailles Run, to name a few, and always sporting T-shirts with the *Imagine* colors.

Every one of your acts of generosity directly affects the scientists and caregivers at *Imagine*, and constitutes a formidable form of encouragement in their daily efforts to combat the disease.

Imagine sets sail with Corentin Douguet © Alexis Courcoux

Imagine Sports Association

Partners and individuals committed to advancing research

Imagine also knows that it can count on the initiatives of its partner companies and patrons. For example, **Antoine Ramponi** wanted to get his company involved alongside *Imagine*. In June 2019, he invited his teams to take part in the Course des Héros. He mobilized 11 participants and for each participant his company donated €l00. *"Everyone was very proud to be involved in this cause and I strongly recommend other companies to have this experience."*

This year, **Havas** continued to advise the Institute and help it throughout the year, notably in deploying its awareness campaigns.

During its international show, the 'Saut Hermès au Grand Palais' from March 22 to 24, 2019, **Maison Hermès** invited its guests to make a donation to the *Imagine* Institute, and made a donation itself.

As for the **Bettencourt Schueller Foundation**, it has been an honorary patron of *Imagine* since 2012. As such, it contributes significantly to the Institute's teaching and training mission. In 2019, the foundation supported the Bioentrepreneurs Program, the International PhD Program, which offers PhD scholarships to highly motivated and talented international students, the Health-Science (MD-PhD) Program, which supports young doctors in their research projects, and the Protected Time in Research Program, intended to strengthen the links between basic research and clinical research.

On December 3, *Imagine* thanked its donors during a convivial 'Giving Tuesday' evening event. After a poignant testimony from Laurence Bergugnat from the 'A future for Margot' association, everyone was able to discuss their commitment to the *Imagine* Institute.

FIRST NAMING CEREMONY AT IMAGINE

On December 19, 2019, *Imagine* brought together the major donors who contributed to the acquisition of NovaSeq around Fati & Michel Rosenberg, on the initiative of an incredible surge of generosity at the *Heroes* III Gala, which means the Institute now has a very high-throughput DNA sequencer thereby considerably increasing its capacity to diagnose genetic diseases.

Faithful supporters of *Imagine*, Fati and Michel Rosenberg, are essential members of the *Heroes* Gala, a charity sale initiated in 2015 by gallery owner Kamel Mennour for *Imagine*.

Moreover, the entire *Heroes* committee mobilized strongly throughout the second half of 2019 in view of a new edition, which, due to the COVID-19 crisis, could not be held at the end of March 2020 as initially planned, and will therefore be postponed.

"We are extremely sensitive not only to the distress of children and families affected by genetic diseases, but also to the excellence of the researchers and doctors who fight every day at Imagine to treat them. We know that the first step is diagnosis. Giving a name to the child's illness is a huge hope for families. Because naming means treatment can begin," recalled Fati and Michel Rosenberg during this ceremony.

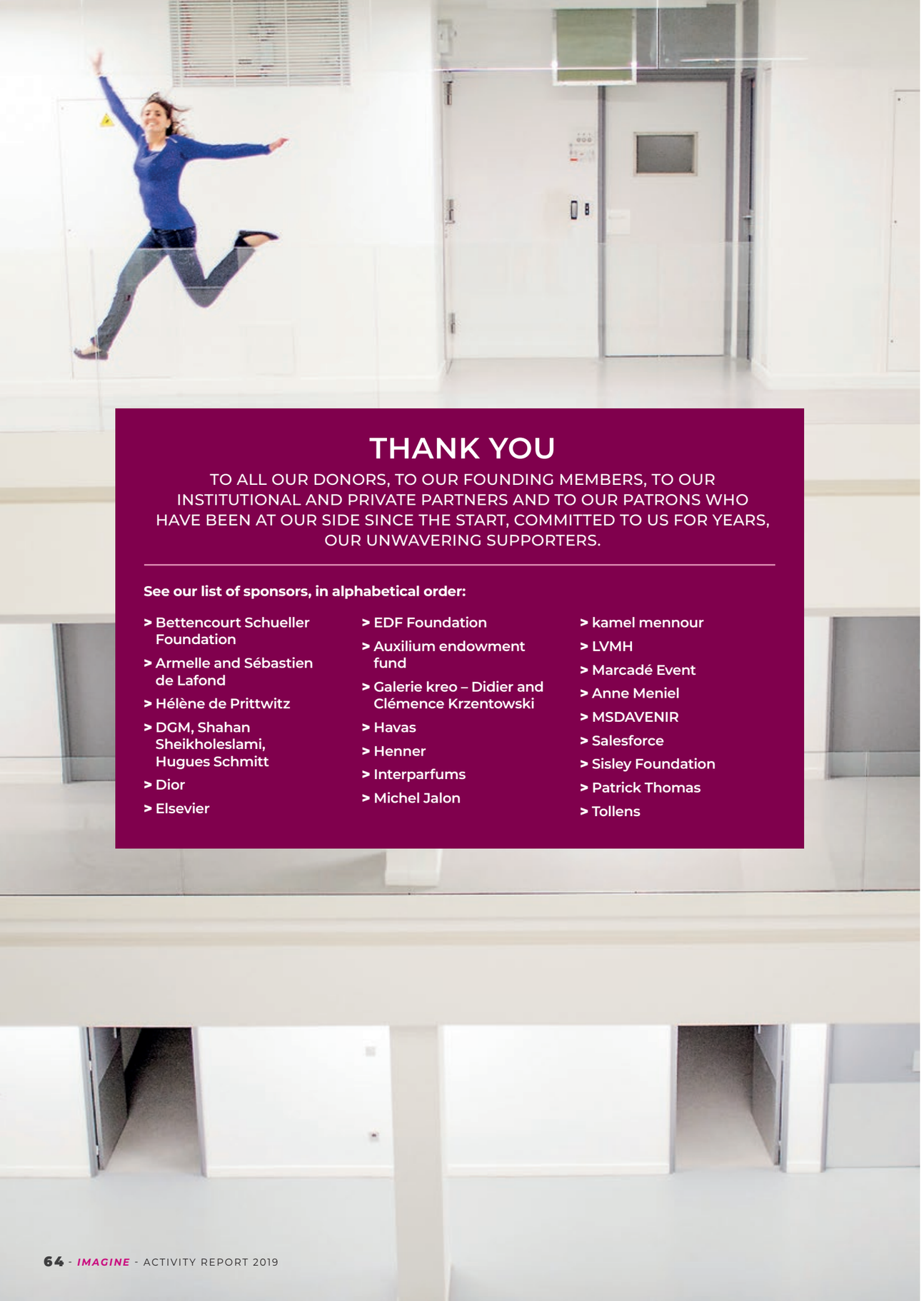
Committed founding members

The *Imagine* Institute is supported by a Scientific Cooperation Foundation. This structure makes it possible to bring together private and public partners and offers them the flexibility and responsiveness essential to accelerating research into genetic diseases. *Imagine* has been supported since its creation by six founding members: AP-HP (Paris Public Hospitals Group), Inserm, Université de Paris, Hospitals of Paris-Hospitals of France Foundation, Paris City Hall, AFM-Téléthon.

After being the first certified University Hospital Institute (IHU) structure in 2011, *Imagine* saw its label renewed until 2024 under the Investments for the Future Program, giving it a so-called acceleration budget of €17 million for the period 2020–2024. This endowment provides its research teams with the best talent and equipment to multiply discoveries for the benefit of patients.

"Imagine *is deeply grateful for the commitment of the nation through the decision of the Prime Minister and the funding granted. In a very competitive context, under the aegis of a demanding international jury, these are great pledges of confidence, acknowledging our scientific and medical results and innovations made thanks to investments in the future and Imagine's public-private agility model,*" says Stanislas Lyonnet, director of *Imagine*.

It is difficult not to conclude this chapter on commitment without mentioning the tremendous wave of solidarity that has taken hold of *Imagine* as we write this report in the midst of the COVID-19 crisis. Given their expertise and know-how, five laboratories and two platforms of the *Imagine* Institute were immediately enlisted in this battle. **They are using their knowledge of genetic diseases to try to better understand COVID-19**, which has aspects reminiscent of certain abnormal immune reactions they have already studied in other circumstances. Some medical researchers have returned to hospital departments, in addition to emergency and resuscitation services on our campus. Thank you to them for their commitment and to everyone for coping with this unique situation as best as possible.



THANK YOU

TO ALL OUR DONORS, TO OUR FOUNDING MEMBERS, TO OUR INSTITUTIONAL AND PRIVATE PARTNERS AND TO OUR PATRONS WHO HAVE BEEN AT OUR SIDE SINCE THE START, COMMITTED TO US FOR YEARS, OUR UNWAVERING SUPPORTERS.

See our list of sponsors, in alphabetical order:

- > Bettencourt Schueller Foundation
- > Armelle and Sébastien de Lafond
- > Hélène de Prittwitz
- > DGM, Shahan Sheikholeslami, Hugues Schmitt
- > Dior
- > Elsevier
- > EDF Foundation
- > Auxilium endowment fund
- > Galerie kreo – Didier and Clémence Krzentowski
- > Havas
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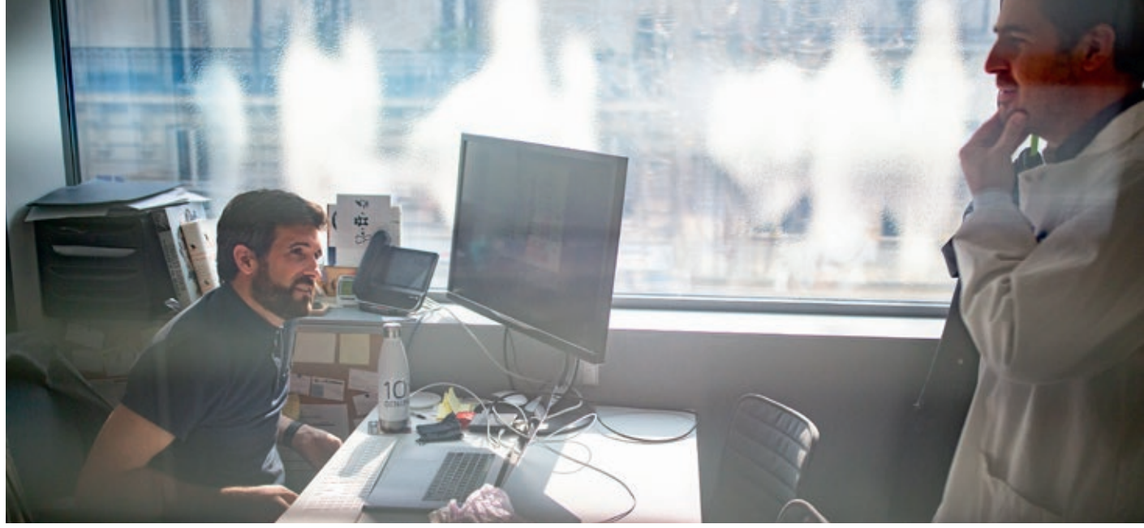

OUR FINANCES

THIS IS THE TWELFTH FINANCIAL YEAR FOR *IMAGINE*.

2019 was a pivotal year for the *Imagine* Foundation as a Hospital-University Institute, an assessment year for the IHU, based on the key achievements of its program certified in 2011 as part of the Investments for the Future Program. French Prime Minister Édouard Philippe wished to renew his confidence in this innovative model by entrusting the National Research Agency with the assessment of these IHUs. In November 2019, the latter announced the extension of the *Imagine* IHU label and five other IHUs for the period 2020–2024, awarding *Imagine* an additional €17 million over this period. The international jury praised the Institute's dynamic, which it described as "one of the world's leaders in genetic research and the treatment of rare genetic diseases," highlighting the scientific excellence of its work, an essential prerequisite for the financial sustainability of the Institute's fundraising trajectory.

Furthermore, the Institute, which has held the 'Tremplin Carnot' label since 2016, submitted a bid for the 'Carnot Institute' label in September 2019. At the time of writing this report, the success of its application in early 2020 validates its ability to develop partnerships with the socio-economic world.

This sixth year of operation since the opening of the building has seen significant achievements in terms of research, innovation and training activities: obtaining two large-scale European 'ERC' programs; obtaining a second university-hospital research program funded by the ANR-PIA (RHU4) on immune deficiencies; and a significant contribution to two other projects that were winners of the same call for projects RHU4. 2019 was also a busy year in terms of the execution of the transverse projects initiated in previous years; on ciliopathies under RHU3, on development anomalies under the DEVO-DECODE project funded by MSD-Avenir; and in Gene Therapy, under the Major Area of Interest Program funded by the Ile-de-France region.

The data science and IRM3T platforms were strengthened and the single-cell analysis platform was launched and certified by the Sésame Filière PIA Program funded by the region and BPI France. 2019 was also the continuation of the Institute's collaborative programs: Cross-Lab and Innogrant. Research and the research-based training program continued its momentum and the Foundation launched a new societal and social sciences and humanities program.

2019 saw the completion of the appraisal of the flagship financial accelerator and expertise project, launched at the end of the financial year and whose implementation will begin in the next financial year.

Finally, the Foundation was able to confirm its industrial partnership dynamic and its ability to convince major donors with the launch of its new fundraising campaign, generating significant initial results around its new campaign president. These results partially offset the loss of revenue related to the postponement of the *Heroes* Charity Gala, initially scheduled for late 2019, and postponed to 2020, with the financial year consequently breaking even. This result should be considered with regard to the surpluses of previous years and the resulting retained earnings.

The overall analysis of the 2019 accounts shows the following figures.

Balance sheet

It should be noted, the balance sheet is a summary statement that makes it possible to describe in terms of applications and resources the financial position of *Imagine* on the closing date of the accounts, i.e. December 31, 2019.

At that date, it stood at **€35,821,909** compared with **€35,866,105** in 2018, i.e. almost zero change, reversals of dedicated funds being fully offset by the increase in investment grants and deferred income on industrial contracts, recorded as liabilities of the institute.

On December 31, 2019, *Imagine*'s assets were as follows in €:

Net assets	12/31/2018	12/31/2019	%
Fixed assets	€9,036,934	€7,338,006	-19%
Current assets	€26,829,172	€28,483,903	6%
Total	**€35,866,106**	**€35,821,909**	**0%**

Net liability	12/31/2018	12/31/2019	%
Associative funds	€17,695,296	€18,750,101	6%
Provision for liabilities and charges	€936,609	€992,290	6%
Dedicated funds	€8,975,106	€6,848,652	-24%
Debts	€8,259,094	€9,230,867	12%
Total	**€35,866,105**	**€35,821,910**	**0%**

Net assets	Net liability
1. Fixed assets: Representing intangible, tangible (and in particular technological platform equipment) and financial assets	**3. Association funds:** DInitial and additional allocation, retained earnings, profit for the financial year and investment grants
2. Current assets: Representing cash, transferable securities and receivables	**4. Provisions for risks and charges:** VAT provision and retirement benefit
	5. Dedicated funds: Resources allocated on operating grants and products resulting from public generosity
	6. Debts: Trade payables, tax and social security liabilities, deferred income and bank overdrafts

Intangible and tangible fixed assets

Fixed assets amounted to €21.46 million at the end of 2019 (compared with €20.77 million in 2018), including €14.62 million in laboratory equipment. The net value of fixed assets decreased in 2019 due to a dynamic depreciation policy (shortening of the depreciation periods for the new genomic sequencer) combined with lower acquisitions of fixed assets in 2019.

Financial fixed assets

In 2019, Step Pharma, in which *Imagine* holds shares, is still yet to generate revenue at its stage of development, and is pursuing an active research and development policy to which it allocates all its funding. In view of these elements and as a precautionary principle, the securities held were depreciated by €208 thousand in 2019, thereby bringing the provision to €358 thousand.

Receivables

Trade receivables amounted to €3.43 million, up by €502 thousand, mainly due to the conclusion of new industrial contracts at the financial year-end.

Other receivables amounted to €4.06 million in 2019. They mainly consist of VAT credit and increased by €1,434 thousand compared to December 31, 2018, following the inclusion of grants to be received for €772 thousand for the 2017 and 2019 installments from the Gene Therapy Major Area of Interest for which the Foundation received approval for funding earmarked for new equipment acquired in 2018 and 2019.

Equity capital

The Foundation's associative funds consist of its initial endowment, fully reconstituted to the amount of €12.9 million at the end of the 2017 financial statements, retained earnings from previous financial years, amounting to €2.89 million, income for 2019 (+€0.12 million) and investment grants received by the Foundation (net value of €2.84 million).

Associative funds total €18.75 million and will increase significantly in 2019 by accounting for investment grants – grants received on the one hand, in regularization, and grants to be received on the other hand – corresponding to the financing duly validated by the Ile-de-France region of fixed assets acquired in 2018 and 2019 by the Foundation under the 2017, 2018 and 2019 installments for DIM gene therapy.

Dedicated funds

In accordance with the accounting plan of associations and foundations, dedicated funds are the liability section which records, at the end of the financial year, the part of the resources allocated by third-party funders to defined projects, the execution of which is in progress, in accordance with the commitment made to them, and of which the unused balance not consumed must be confirmed in the accounts. They amounted to €6.85 million at the end of 2019 and were made up for €3.16 million of provisions made on the non-expendable ANR-IHU allocation (decreasing, linked to the acceleration of the execution of the IHU program), for €1.65 million on other public grants (a significant increase linked to new grants obtained within the framework of ANR's generic calls for projects) and for €2.04 million of those made up of earmarked donations.

Debts

Debts amount to €9.23 million, in respect of supplier debts (€ 4.26 million, slightly down), tax and social security debts (€ 1.63 million), assets to be paid (€ 0.57m) and revenue recognized in advance on industrial contracts. The latter increased by 31%, from €2,216,091 in 2018 to €2,769,637 in 2019, marking the continued increase in these contracts.

Income statement

For the record, the 2019 income statement covers all the flows that positively or negatively alter the financial situation of *Imagine* in 2019, tracing the products that generate wealth and the expenses that reduce it by enabling the activity of the Institute.

The income statement of *Imagine* is as follows:

- **Products: €26,692,829** (compared with €22,984,543 in 2018,18,349,515 in 2017; €16,801,238 in 2016 and €19,155,981 in 2015),
- **Charges: €26,570,383** (compared to €22,014,465 in 2018; €16,959,388 in 2017; €14,841,491 in 2016; and €14,373,478 in 2015).

The surplus was €122,446 in 2019 compared with a profit of €970,078 in 2018.

	12/31/2018	12/31/2019	%	Change
TOTAL INCOME	€22,984,543	€26,692,829	16%	€3,708,286
TOTAL EXPENSES	€22,014,465	€26,570,383	21%	€4,555,918
RESULT	**€970,078**	**€122,446**		

2019 Products

Imagine's income grew by 16% in 2019: from €10 million in 2014 to €19.1 million in 2015 (including €1.2 million from the regularization of the VAT recovery on purchases in previous years and €2.4 million from the reversal on dedicated funds), then reduced to €16.8 million in 2016, reaching €18.3 million in 2017, €22.98 million in 2018 and **€26.69 million in 2019.**

Their growth was driven by reversals of dedicated funds, which rose from €3.44 million to €8.92 million in 2019) and that of public grants (€6.40 million in PIA grants and €2.93 million in other grants, up 29%). Revenue growth from industrial contracts continues to contribute to this change (nearly €3 million). All of these positive developments more than offset the observed and expected fall in donations (see below).

Income for the year breaks down into operating income, financial income and extraordinary income.

Operating income increased from €9 million in 2014; €14.8 million in 2015; €14.4 million in 2016; €15 million in 2017; and €18.9 million in 2018; it amounted to €17.04 million in 2019 despite the postponement of the Heroes Charity Gala, of which 2018 was marked by the excellent results of the third edition and the correction of previous errors burdening the amount of operating grants in favor of investment grants recorded in shareholders' equity (switch of €196 thousand).

Services sold continued to grow, increasing from €1.2 million in 2015; to €1.9 million in 2016; €2.46 million in 2017; €2.89 million in 2018; to €2.93 million in 2019, due to the momentum of industrial partnerships (€1.1 million in 2016; €1.7 million in 2017, €1.9 million in 2018 and €2 million in 2019, plus €2.8 million deferred income valid for 2020).

Donations fell compared to previous years, returning to the 2017 level in 2019 (€3.32 million). The 'other income' item that traces them back to the income statement must be analyzed in light of the difference of the Heroes Charity Gala that marked the 2018 results.

Financial income fell slightly in 2019 against a backdrop of general gloom in the money markets (€32,873 in 2019 compared with €72,928 in 2018; €91,004 in 2017; €44,514 in 2016; €50,672 in 2015; and €71,451 in 2014). The healthy situation of the Institute's treasury, and its liquidity, allows it the management agility necessary to maintain the pace of project development. The institute nevertheless wishes to conduct an in-depth investigation in 2020 in order to establish a piloting plan at an infra-annual rate, the only way capable of identifying any potential for additional placements.

Exceptional income of €696,726, corresponds to the share of investment grants previously recognized in profit or loss, the natural decrease of which is more than offset in 2019 by the inclusion of a new investment grant as part of the 2019 installment of DIM Gene Therapy.

2019 expenses

The Foundation's expenses increased by 21% in 2019, reaching €26.57 million compared with €22 million in 2018; €16.6 million in 2017; €14.8 million in 2016; and €14.4 million in 2015. They break down into operating expenses, financial expenses and extraordinary expenses.

Their 2019 growth rate is driven by allocations to dedicated funds (effect of new grants, in particular ANR, and the effect of new earmarked donations). The neutralization of these shows a 15% increase in current expenditure in 2019.

Operating expenses reached €19.54 million in 2019; compared with €17.1 million in 2018; compared with €13.8 million in 2017; €12.9 million in 2016 and le €10.4 million in 2015.

They reflect the increase in the Institute's current operating expenses (+€2.5 million) directly linked to the development of contracts hosted for industrial partnerships or public grants and the actions carried out under the IHU program as provided for in its roadmap and presented in the introduction of this report.

This dynamic is directly reflected in the €1.4 million increase in staff expenses between 2018 and 2019 (+20% on average, +44% on hosted contracts, strong growth elsewhere concerning platforms), with other expenses (services, consumables and grants) increasing in parallel by 16%, driven by grants paid to partners of the DIM and RHU projects. The latter are included for €0.86 million in the 'grants granted by the association' for which they explain the jump in 2019. However, depreciation was virtually stable in 2019 (€2.2 million).

The **financial and exceptional expenses** represent accounting transactions and vary between 2018 and 2019 by €208 thousand due to the recognition of a provision for the impairment of investments in Step Pharma, explained on page 3 of this report.

The set of **reversals and allocations to dedicated funds** directly reflects the acceleration of the implementation of programs with earmarked funding from the Institute.

The **result** for the financial year is very slightly in surplus, at €122 thousand, and must be analyzed with regard to the kinetics of fundraising operations as well as previous surpluses, which also reflect the latter.

Annual use of funds statement

This annual use of funds statement describes the allocation of funds collected from the public by type of fund, and traces the contribution of donations to the scientific project.

Total funds break down to: 87% on social missions, 4% on fundraising costs and 9% on all operating costs.

Donations collected in 2019 amounted to €3,317,803 and were supplemented by a variation in dedicated funds of €281,305, corresponding to the retention of donations collected in previous years (€ 2,274,574), partially used in 2019, and hence the carryover to the 2020 financial year of 1,993,270 euros. Consequently, the resources collected from the public and used in 2019 total €3,599,108 and are broken down as follows:

a. Social missions €3,239,197 (90%)

b. Costs of appealing to public generosity €179,955 (5%)

c. Operating expenses €179,955 (5%)

Caroline YOUNG, Treasurer

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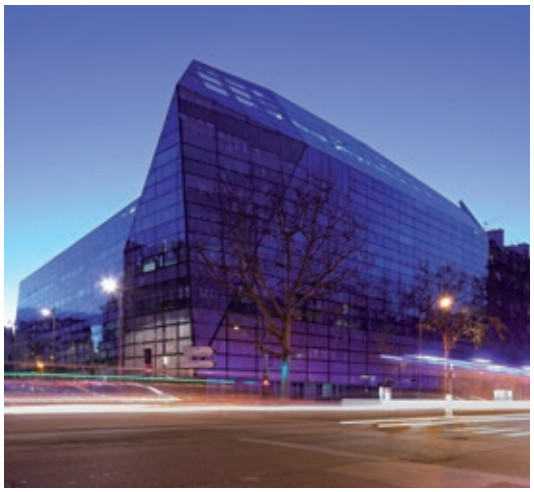

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