imagine

INSTITUTE OF GENETIC DISEASES

Imagine, curing genetic diseases

2018 ANNUAL REPORT

Imagine, a brief history

2007
- Creation of the *Imagine* Foundation, Scientific Cooperation Foundation (FCS) dedicated to genetic diseases, by Prof. Alain Fischer, Claude Griscelli, Arnold Munnich and Stanislas Lyonnet notably.
- 6 founding members to identify, understand, treat, transfer and share.

2008
- 1st recruitments, 1st core facilities and 1st equipment.

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

2011
- IHU accreditation (French University Hospital Institute), in the context of the French Investments for the Future Program, bringing together 20 research teams, 12 reference centers for rare diseases and 6 clinical departments at Hôpital Necker-Enfants malades AP-HP.
- 1st call for applicants for the MD-PhD program.

2012
- 1st three *Imagine* teams recruited internationally.

2013
- 1st call for applicants for the "Time for Research" program.

2014
- Opening of the *Imagine* building.
- Accreditation of the Joint Research Unit (UMR) Inserm / Université Paris Descartes merging 20 existing teams.
- Affiliation of the 1st two partner labs within Hôpital Necker-Enfants maladies AP-HP.

2015
- 1st edition of the Heroes charity gala.
- 1st call for applicants for the international PhD program.

2016
- Prof. Stanislas Lyonnet takes over from Prof. Alain Fischer as Director of *Imagine*, and Prof. Arnold Munnich takes over from Prof. Claude Griscelli as President of the *Imagine* Foundation.
- 1st class of students on the Masters in Bioentrepreneurship.
- ANR Tremplin Carnot status.

2017
- Creation of the custom-made Dior chair for tailored medicine at *Imagine*.
- Launch of the RHU C'IL LICO "Medicine of the future for ciliopathies with renal failure".
- Domaine d'Intérêt Majeur (DIM) [Area of Major Interest] accreditation by the Ile-de-France (Greater Paris) region for gene therapy.
- Recruitment of the 8th *Imagine* team.

2018
- Assessment of the Institute's 24 research laboratories by HCERES (High Council for the Assessment of Research and Higher Education).
- From 15 to 25 reference centers for rare diseases on campus at Hôpital Necker-Enfants malades AP-HP affiliated with *Imagine*, and 4 partner labs.

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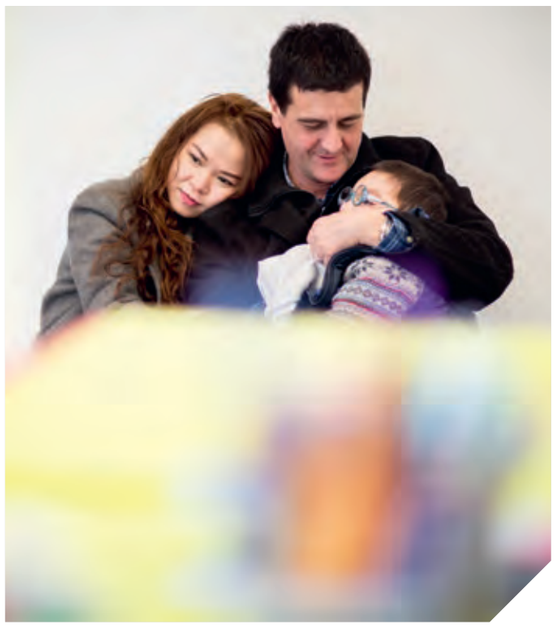


Joint interviews

What were the highlights of 2018?

Prof. Stanislas Lyonnet, **Director of the *Imagine* Institute:** *2018 was an exciting year for the Imagine Institute. After our Scientific Advisory Board (SAB), the scientific groups of our Joint Research Unit were assessed by the expert committees of HCERES (High Council for the Assessment of Research and Higher Education), Inserm and Université Paris Descartes. HCERES pointed out that the strength of our Institute, a unique initiative in Europe and worldwide (in their own words), above all is its ability to be patient-centered and include clinicians in fundamental research teams. Recommendations issued by these experts, as well as those from our SAB, renewed with three new members during its annual visit in October, provided a basis for developing our project for the next ten years (“*Imagine *18-28”). As you will discover in this report, 2018 was also marked by high-quality scientific publications, and by major advances in research and treatments. My sincere thanks to every single member of* Imagine*, as well as every partner and sponsor who, thanks to their support, have contributed to these discoveries.*

Laure Boquet, General Delegate of the *Imagine* Institute: *2018 is a milestone in our Institute’s acceleration strategy to bolster research on genetic diseases. Once again, this year demonstrated all the qualities of our public-private model. The public and private founding members of the* Imagine *Institute have expressed their trust and commitment to us by renewing the multi-year agreements for five years, which connects us to each of them, as well as by working alongside us to properly and correctly implement the initiatives in our strategic roadmap. Our private partners, benefactors and sponsors, also play a crucial role in the Institute’s development. Their attention, as demanding as it is caring, is a tremendous driving force to implement the projects in our roadmap as effectively as possible. First among these, the Fondation Bettencourt Schueller which funds half of our education program through and for research. As for the roll-out of the medicine of tomorrow, it is accompanied by the Christian Dior Couture House through a chair. Not forgetting our Benefit Committee, which helped with the organization and the magnificent success of the 3rd edition of our Heroes charity gala. We raised €7 million to fund our innovative research projects, and specifically to purchase the latest generation very high-throughput sequencer, creating more prospects in terms of diagnosis. They also contribute to Imagine’s “singular and unique character”, to reflect the terms of our Scientific Advisory Board last October, welcoming as much clinical/research integration as possible within the Institute.*

Rooted in Ile-de-France - the Greater Paris region - *Imagine* is an Institute that is open to its ecosystem and internationally minded. What were the highlights of this opening in 2018?

Laure Boquet: *The connections and relations between our doctors and researchers, the patients and their associations, our campus and our partners have been enhanced. The Institute achieved its intention to open near Hôpital Necker-Enfants malades campus and AP-HP, with the affiliation of ten new reference centers for rare diseases at* Imagine*, bringing the number of reference centers at the Institute to 25, and increasing the teams’ capabilities to conduct clinical research projects. In addition, opening a collaborative space dedicated to* Imagine*’s and its founding members technology transfer structures, and to the installation of the French health innovation entrepreneurs association, France Biotech, should accelerate value creation. The results regarding industrial partnerships, patents filed and contractualization of licenses show the Institute’s potential on this front.*

Letter from the founding chairman

Prof. Arnold Munnich, President of the *Imagine* Foundation: *A pioneer and singular Institute in Europe,* Imagine *has to share its model internationally, attract researchers and collaborate globally. In this perspective, this year the Institute signed international collaboration agreements, hosted visits from international universities, research centers and hospitals looking ahead towards future collaborations. The first editions of the Eurodis Winter School on innovation and translational research and the international conference on gene therapy, Gene Therapy Partnering Day, were organized at* Imagine*, always aiming to accelerate discoveries and their application for patients.*

What are the challenges for the years ahead?

Prof. Stanislas Lyonnet: *At the time of writing this report, all members of Imagine are highly mobilized by the Institute’s application to extend its status and funding as a University Hospital Institute (IHU) for the next five years. Against this background, the Institute is focused on new objectives which will provide us with direction for the next ten years (*Imagine *18-28 project). Our top priority is to maintain and even increase scientific excellence intended to radically improve the diagnosis and treatment of patients, offering a better life to them and their family. With this in mind, our commitment for the next 10 years is to double the number of children diagnosed, double leads and research projects on the mechanisms of their diseases, double inclusions in clinical trials, and double the innovative solutions available to them.*

Prof. Arnold Munnich: *To change things in the years ahead, we will focus on continuing to open our accelerator model beyond our institutional, clinical and geographical boundaries. After 10 years of existence, the* Imagine *Foundation’s goal is to tackle global science through the creation of an international network and a team effort at a European and global level. For that reason,* Imagine *will focus on its international appeal and visibility. Appeal to attract the best talent, recruit teams, organize international programs. Visibility to implement our projects and collaborations worldwide.*

“The pride of the Institute is that here, everyone unanimously thinks the same thing: the virtuous circle that we wanted, which goes from the patient and comes back to them to cure them or at least give them relief, is done daily at Imagine, with unquestionable success. For this excellence to exist and continue, it needs to be assessed at the highest level, but it also needs to offer optimum working conditions to our teams so their creativity and their expertise is leveraged for our patients, bringing with them the joy of life and discovery.”

Prof. Claude Griscelli, Founding chairman of Imagine *Institute*

Imagine, leading european center for research and care in genetic diseases

2018 FIGURES

860 SCIENTIFIC PUBLICATIONS

46 ACTIVE PATENTS AND PROPRIETARY SOFTWARE PROGRAMS

900 RESEARCH AND HEALTH STAFF GATHERED AROUND THE SAME CAUSE

35 NATIONALITIES

4 M€ THROUGH INDUSTRIAL PARTNERSHIPS

More than 6 M€ RAISED (GIFTS, GRANTS AND PHILANTHROPY)

28% DE DOCTORANTS, POST-DOCTORANTS ET ÉTUDIANTS

15 CORE FACILITIES

5 ERC (EUROPEAN RESEARCH GRANTS)

24 24 RESEARCH GROUPS ON SITE

4 ASSOCIATED LABORATORIES AT NECKER-ENFANTS MALADES HOSPITAL

580 ONGOING CLINICAL STUDIES IN THE IHU PERIMETER

6 INTEGRATED CARE AND RESEARCH PROGRAMS (ICARPS)

CLINICIANS

25 REFERENCE CENTERS FOR RARE DISEASES

6 HOSPITAL UNITS

2 CLINICAL INVESTIGATION CENTERS

PATIENTS AND FAMILIES

MORE THAN **30,000** CONSULTATIONS ON SITE

BIOBANK

100,000 SAMPLES

IMAGINE'S 6 FOUNDING MEMBERS:

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Inserm
La science pour la santé
From science to health

UNIVERSITÉ PARIS DESCARTES

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

AFMTÉLÉTHON
INNOVER POUR GUERIR

iCARPs, an accelerator for research and care

- Reference centers of rare diseases and clinical departments of the Necker-Enfants malades Hospital
- Research laboratories
- Associated laboratories

NEPHROLOGY

- **S. SAUNIER & C. ANTIGNAC:** Hereditary kidney diseases
- **M. SIMONS:** Epithelial biology and disease
- **C. LEGENDRE:** Nephro-transplantation Department
- **R. SALOMON:** Hereditary kidney diseases of the child and the adult
- **R. SALOMON:** Pediatric nephrology Department

NEURO-DEVELOPMENT

- **N. BODDAERT:** Image@*Imagine*: multimodal brain imaging research
- **V. CANTAGREL:** Developmental brain disorders
- **E. KABASHI:** Translational research for neurological disorders
- **A. PIERANI:** Genetics and development of the cerebral cortex
- **A. RÖTIG:** Genetics of mitochondrial diseases
- **JM. ROZET:** Genetics in ophtalmology
- **N. BAHI-BUISSON:** DI-Rett Center
- **D. BRÉMOND-GIGNAC:** Rare ophtalmological diseases
- **P. DE LONLAY:** Hereditary metabolic diseases
- **A. MUNNICH:** Mitochondrial diseases
- **R. NABBOUT:** Rare epilepsies
- **M. RIO:** Intellectual disabilities of rare causes

IMMUNOLOGY-INFECTIOLOGY-GASTRO

- **L. ABEL:** Human genetics of infectious diseases : complex predisposition
- **JL. CASANOVA:** Human genetics of infectious diseases: monogenic predisposition
- **N. CERF-BENSUSSAN:** Intestinal immunity
- **Y. CROW:** Neurogenetics and neuroinflammation
- **S. LATOUR:** Lymphocyte activation and susceptibility to EBV
- **M. MÉNAGER:** Inflammatory responses and transcriptomic networks in diseases
- **G. MÉNASCHÉ & F. SEPULVEDA:** Molecular basis of altered immune homeostasis
- **F. RIEUX-LAUCAT:** Immunogenetics of pediatric autoimmune diseases
- **JP. DE VILLARTAY & P. REVY:** Genome Dynamics in the Immune System
- **S. BLANCHE:** Immuno-hematology and pediatric rheumatology Department
- **A. FISCHER:** Hereditary immuno-deficiencies
- **O. GOULET:** Rare digestive tract diseases
- **O. LORTHOLARY:** Infectious and tropical diseases Department
- **P. QUARTIER DIT MAIRE:** Juvenile arthritis

HEMATOLOGY

- **I. ANDRÉ & M. CAVAZZANA:** Hematopoietic disorders: from deciphering the mechanisms to innovative therapies
- **O. HERMINE:** Molecular mechanisms of hematologic disorders and therapeutic implications
- **A. MICCIO:** Chromatin and gene regulation during development
- **M. CAVAZZANA:** Innovative therapy Department
- **A. HARROCHE:** Pediatric hemophilia
- **O. HERMINE:** Mastocytosis
- **O. HERMINE:** Adult hematology Department
- **M. DE MONTALEMBERT:** Major sickle cell syndromes

COMPUTATIONAL DECISION-SUPPORT SYSTEMS

- **A. RAUSELL:** Clinical bioinformatics
- **JP. BONNEFONT:** Medical Genetics Federation
- **A. BURGUN:** Medical informatics Department

DEVELOPMENT & CARDIOLOGY

- **M. POLAK:** Molecular basis of several congenital or neonatal endocrine disorders and establishment of new therapeutic strategies
- **S. SARNACKI & I. BLOCH** (Télécom ParisTech) Computational anatomy for image-guided minimally invasive surgery in pediatric tumoral and developmental diseases
- **Y. VILLE:** Impact@*Imagine* – innovative multidisciplinary prenatal approach of congenital diseases and their treatments
- **J. AMIEL & S. LYONNET:** Embryology and genetics of malformations
- **A. HOVNANIAN:** Genetic skin diseases : from disease mechanism to therapy
- **L. LEGEAI-MALLET & V. CORMIER-DAIRE:** Molecular and physiopathological bases of osteochondrodysplasia
- **S. MEILHAC:** Heart Morphogenesis
- **V. ABADIE:** Pierre Robin Sequence
- **J. AMIEL:** Developmental abnormalities and malformation syndromes
- **C. BODEMER:** Genetic diseases with cutaneous expression
- **D. BONNET:** Complex congenital heart defects
- **V. CORMIER-DAIRE:** Constitutional bone diseases
- **F. DENOYELLE:** Rare ENT malformations
- **S. MARLIN:** Genetic deafness
- **A. PICARD:** Cranial and facial malformations
- **M. POLAK:** Rare gynecological pathologies
- **S. SARNACKI:** Rare anorectal and pelvic anomalies
- **M. ZERAH:** Craniosynostosis
- **M. ZERAH:** Vertebral and spinal malformations

Clinical and technological base

CLINICAL RESOURCES OF NECKER-ENFANTS MALADES HOSPITAL

1 Clinical Investigation Center (JM. Tréluyer)
1 biotherapy center (M. Cavazzana)

SUPPORT PLATFORM FOR RESEARCH (*IMAGINE*)

1 Investigation team
1 Promotion team

15 CORE FACILITIES

Imagine: Data Science, IPS (induced pluripotent cells), Transgenesis, Translational Genetics, rAAV vectors, Imaging IRM3T.

SFR Necker/*Imagine:* Genomic, Bioinformatics, DNA biobank, Proteomic, Cytometry, Cell imaging, Histology, Viral vectors and gene transfer, Animal experimentation and transgenesis.

Our governance

The *Imagine* Institute is governed as a **Scientific Cooperation Foundation (FCS) established in 2007**. The FCS is a private body the objective of which is to facilitate public-private partnerships and to manage public and private funds. The Institute opted for this status in the interests of maximum agility and responsiveness, combining the best that both the public and private sectors have to offer, the goal being to accelerate research on genetic diseases.

Imagine was the first structure **approved as a University Hospital Institute** (IHU) in 2011. As such, the Institute receives an endowment of €6.2 million per year, which is awarded until 2020 as part of the **French Investments for the Future Program**. In 2018 and 2019, the Institute applied for a five-year extension of a part of this annual grant (2020-2024). This application will be competitively assessed in 2019.

In 2018, *Imagine* united with 6 other French University Hospital Institutes (ICM, Liryc, IHU Strasbourg Mix-surg, Méditerranée Infection, iCan, FOReSIGHT) under the IHU-France status in order to showcase the innovative character of IHUs, their missions and their latest activities and news.

The Institute has been approved as a **"Tremplin Carnot"** by the French Ministry of Higher Education and Research since 2016. This status is awarded to structures that conduct leading research activities and a proactive partnership research policy simultaneously.

Our founding members:

In 2018, *Imagine* Institute renewed its five-year agreements with its founding members, illustrating their commitment to continue supporting the IHU program and their trust in the *Imagine* Foundation to see it through.

Our governing bodies:

The *Imagine* Foundation has a **Board of Trustees**, with members including the six founding institutions, qualified individuals chosen by the founders, as well as elected representatives of teachers, researchers and research professors. In 2018 the Board of Trustees met twice and welcomed 4 new qualified individuals in December.

The Director of the Institute is supported by a mixed **Executive Committee** made up of representatives of researchers and clinicians from various research and care programs. The committee meets twice a month to establish the Institute's main strategic guidelines.

The **IHU Board of Management** brings together laboratory directors and staff representatives aimed at discussing the main scientific guidelines, the organization and life at the Institute, as well as research resources. It met 4 times in 2018.

Scientific Advisory Board

Made up of eminent global scientists, the Scientific Advisory Board (SAB) makes recommendations each year to the Board of Trustees and to *Imagine*'s top Management on the Institute's scientific and strategic guidelines, including the selection of new teams, the development and organization of scientific groups, as well as the assessment of their work.

In 2018, three new members joined this committee: **Iain Drummond** of Harvard Medical School, **Bernard Malissen** of the Marseille-Luminy immunophenomics center, and **Antoine Triller** of the Ecole Normale Supérieure Institute of Biology.

SAB COMPOSITION:

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

Prof. Stylianos Antonarakis
Division of Medical Genetics,University of Geneva, Medical School, Geneva, Switzerland

Prof. Aravinda Chakravarti
Institute of Genetic Medicine, John Hopkins University School of Medicine, Baltimore, USA

Iain Drummond
Division of Nephrology, Massachussets General Hospital,
Department of Genetics, Harvard Medical School, USA
Harvard Stem Cell Institute Kidney Program

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

Bernard Malissen
Director of the Immunophenomics Center, Marseille-Luminy, France

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

Prof. Fiona Powrie
Experimental Medicine Division,
John Radcliffe Hospital, Oxford, UK

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

The Scientific Advisory Board met at *Imagine* on October 4 and 5, 2018.

Elizabeth Blackburn, SAB President:

"I have been a SAB member for ten years. I have witnessed the Institute's development and the realization of its dream, which was to bring together all the knowledge in developmental sciences and all the expertise regarding understanding genetic diseases, within a single place and with a spirit of synergy. I do not think that this unique compilation could be found elsewhere".

Iain Drummond, new SAB member:

"For basic scientists, the Imagine Institute is a singular and invaluable opportunity to interact with clinicians. I chose to join its Scientific Advisory Board to satisfy my enthusiasm for science, which is about learning from colleagues, sharing knowledge and trying to exceed individual limitations, in a unique Institute that combines genomics and experimental biology".

Highlights

The research quality at *Imagine* commended by HCERES

The HCERES committee (High Council for the Assessment of Research and Higher Education) assessed the UMR1163-*Imagine* Institute (Inserm, Université Paris Descartes) in March 2018. Drafting files then visits from expert committees really mobilized the teams.

Following its assessment, the committee highlighted many positive points and made some recommendations. According to the assessors, the strength of our Institute is its ability to be patient-centered and include clinicians in fundamental research teams.

"The Imagine *Institute is a unique initiative in Europe and worldwide, combining research focused on genomics with a large cohort of patients suffering from rare pediatric diseases at Hôpital Necker-Enfants malades AP-HP. The Institute's teams are world leaders in identifying the genetic causes responsible for infantile diseases. The total scientific publications of the Institute is remarkable when you compare it with international norms. The Institute is a leading global center for the introduction of molecular genetics in clinical care and for training young scientists in the field of molecular genetics. The program for the next five years should make a significant contribution to improving the knowledge and treatment of genetic diseases",* concluded the HCERES assessors.

€7 million raised for "Heroes for *Imagine* III"

A new edition with renewed success for the "Heroes for *Imagine*" gala, which was held on February 12, 2018 and brought together 360 "Heroes". Loyal supporter of *Imagine*, Gad Elmaleh presided as master of ceremonies for this auction which posted a profit of €4.6 million, to which the DEVO-Decode program announcement by MSDAVENIR was added (€2.4 million) for a record €7 million. The sales of this evening initiated by Kamel Mennour, joined by Didier and Clémence Krzentowski, were presided by François de Ricqlès and Julien-Vincent Brunie for Christie's.

Imagine would like to thank the sponsors and collectors, artists and creators, galleries and donors, great houses and well-known figures who are all committed to advancing genetic research.

The funds raised allow *Imagine* to buy state-of-the-art equipment, recruit the best talent and continue its programs of excellence in aid of patients with genetic diseases.

NovaSeq: high-throughput version genomics

In November 2018, thanks to the tremendous generosity of its donors during the Heroes evening, *Imagine* was able to purchase a very high-throughput DNA sequencer, the NovaSeq.

The device offers new prospects in diagnostic research. This cutting-edge technology for exome sequencing, comparing DNA, and whole human genome sequencing, provides data more quickly that is more reliable, better quality, and at a lower cost.

"With the NovaSeq, we will be able to accelerate research on genetic diseases. First, it will allow us to name diseases, leverage diagnostic capabilities, then offer ways to understand diseases and thus therapeutic options", commented Christine Bole-Feysot, Manager of the genomics core facility at *Imagine*.

Prizes and awards

- **Jean-Laurent Casanova:** 2018 "Claude Bernard" Grand Prize of the City of Paris
- **Marina Cavazzana:** Europe Health Prize 1
- **Nadine Cerf Bensussan:** University of Tampere Maki Prize
- **Max Cooper (SAB member):** Winner of the Japan Prize
- **Yanick Crow:** Advanced Grant, "E-T1FNs" project, elaboration of the type I interferonopathies
- **Audrey Desgrange:** L'OREAL-UNESCO France grant for women in science
- **Alain Fischer:** Rank of commander of the French Legion of Honor
- **Marie-Louise Frémond:** French Academy of Medicine winner, Evian-les-Bains Mineral Water Company Prize
- **Johanna Lokmer:** 1st prize young researchers, fundamental research at the European Days of the French Society of Cardiology
- **Bernard Malissen (SAB member):** Medical Research Foundation Grand Prize (Fondation pour la Recherche Médicale)
- **Sigolène Meilhac:** Pasteur Vallery Radot Prize
- **Capucine Picard:** Fondation Guillaumat-Piel Prize from the Medical Research Foundation
- **Sabine Sarnacki:** 2018 Jurain Mondor Prize from the French Academy of Sciences (Académie des Sciences).

Imagine's roadmap...
to name and cure genetic diseases

Since the creation of the *Imagine* Foundation in 2007, the Institute has implemented many structuring cross-disciplinary projects, formalized and developed in the 2016-2025 roadmap signed in December, 2016 by *Imagine* with its founding members. Today, *Imagine* is focused on its ambition to change the lives of families affected by genetic diseases. To this end, the focus is on setting out new objectives which will provide direction over the next ten years.

Taken separately, genetic diseases are very rare, even exceptional, but collectively throughout Europe, they affect 35 million people. In France, 3 million people are affected, nearly 1 in 20 French people. To this public health issue we can add the fact that nearly 50% of these diseases are undiagnosed, and when they are diagnosed, it is most often after months or even years of diagnostic uncertainty.

Since it came into being, *Imagine* has proved its unique capabilities to accelerate innovation, both in diagnosis and treatment. The synergies between doctor and researcher expertise, all in one place, helps us to never give up, to look for the best collaborations and to constantly innovate to overcome genetic diseases.

Today, *Imagine* has all the resources to change things from now to 2025, to diagnose 80% of children with rare genetic diseases, but also to give 30% of them access to treatment.

Imagine, European leader in care and research on genetic diseases

Imagine's strength lies in its research teams, reference centers and clinical departments around patients with genetic diseases to provide them with better care. Since its creation, *Imagine* has already:

- Offered more than 30,000 consultations/year within the reference centers for rare diseases
- Identified more than 250 genes, improving both the diagnosis and the lives of many families
- Developed more than 32 gene panels, diagnosing more than 3,000 diseases
- Completed the 1st global treatments for several pathologies, which are new therapies or a repositioning of molecules that are already used in other pathologies: sickle-cell disease, beta-thalassemia, interferonopathies, etc.
- Collected 50 million pieces of data concerning 680,000 patients, from 5.6 million documents, and structured in a translational research data warehouse on rare diseases, which is there to facilitate advances and discoveries on these pathologies
- Identified 52 therapeutic solutions from now to the pre-clinical or clinical stage
- Performed more than 20,000 DNA sequences
- Enrolled more than 7,000 patients in over 580 clinical trials.

One ambition: to change the lives of families affected by genetic diseases

After a great deal of success, *Imagine* wants to step up its initiatives because there is still a lot to do to name all diseases, to understand them and offer therapeutic solutions to children who are suffering from them.

Imagine's researchers and doctors are therefore continuing their efforts and have set goals from now to 2028 as part of their new roadmap to:

- Double the number of children diagnosed, thereby significantly reducing diagnostic odyssey;
- Double the number of decrypted and recognized mechanisms responsible for these diseases, by recruiting research teams with new expertise;
- Double the number of clinical trials within the reference centers for rare diseases to eventually double therapeutic solutions;
- Find common denominators to treat groups of diseases by targeting common mechanisms;
- Continue to enhance the Institute's exceptional cohorts;
- Expand resources and the return on investment by multiplying funds from industrial partnerships and from the generosity of friends of *Imagine*.

Priority programs to accelerate discoveries

To accelerate innovation for the benefit of patients, *Imagine* has identified priority areas for the next few years (See pages 8-9). To successfully conduct its ambitious projects, *Imagine* knows that it can count on the support of its founding members and on the strength of the synergies between staff in research, health, clinical departments and reference centers on campus at the Hôpital Necker-Enfants malades AP-HP.

Immunology/infectology

Hematology

Nephrology

Neurological diseases

Development and Cardiology

And the latest of these programs:
combining data sciences and computer-aided decisions to build the medicine of tomorrow.

This newly created program brings together the strength and expertise required for its deployment. Thanks to the development of bioinformatics tools and artificial intelligence, its objective is to make the clinical and biological data speak for itself, explore areas still unknown like non-coding DNA regions, analyze pathologies at the level of a single cell to better understand them, and therefore offer customized and progressive care over time.

Discovering

To find the origin of a genetic disease is to already better understand its mechanism

Our goal is to name the disease of each child. Even if it is the only case in the world, we want each pathology to be subject to research at the highest level and each child to know the treatment they will have one day.

Prof. Stanislas Lyonnet, Director of *Imagine* Institute

Dis
cove
ring

o envisage curing a genetic disease, we must first be able to name it and understand its mechanism. Three stages are needed to achieve a diagnosis and then be able to develop a treatment:

1. **IDENTIFY THE GENE(S) RESPONSIBLE FOR THE DISEASE**
2. **MAP OUT THEIR MUTATIONS**
3. **UNDERSTAND THE DISRUPTIONS CAUSED BY THESE MUTATIONS**

"Our little boy is a carrier of a rare genetic disease, which we were able to diagnose at Imagine. We know the importance of research: diagnosing a disease is identifying your enemy and allowing researchers to potentially find the cure one day."

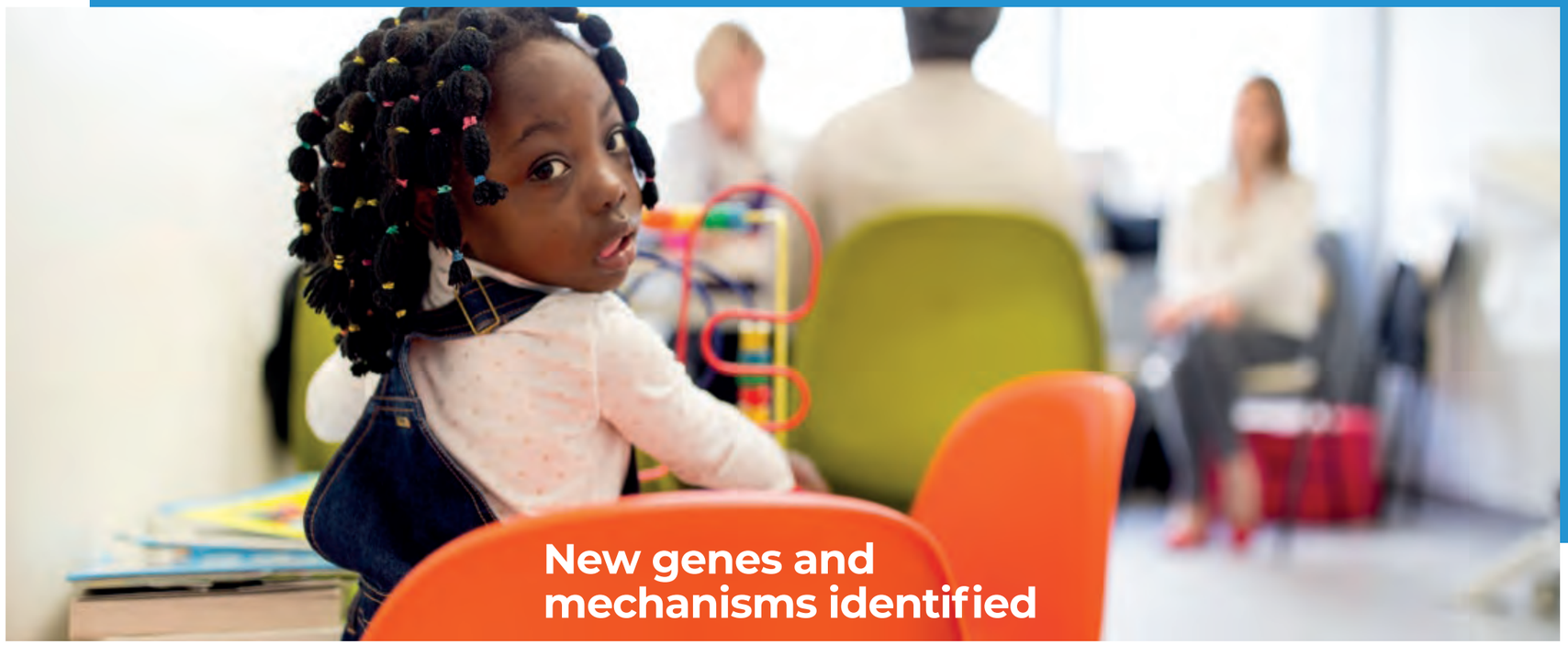
Nadia, mom to a young boy with a genetic disease diagnosed after 6 years of diagnostic uncertainty.

To get there, teams at *Imagine* Institute collaborate within and across disciplines and with a culture of openness. In 2018, the scientific groups of our Joint Research Unit 1163-*Imagine* Institute (Inserm/Université Paris Descartes) were assessed by the expert committees of HCERES (High Council for the Assessment of Research and Higher Education, see page 12), Inserm and Université Paris Descartes, which emphasized the quality of research at *Imagine*.

"Today, 1 child out of 2 welcomed to a genetic consultation at Imagine *and Hôpital Necker-Enfants malades AP-HP still leaves with no diagnosis. Every gene identified is a big step as it allows us to name the disease of a child, even several children"*, outlined Prof. Stanislas Lyonnet, Director of the *Imagine* Institute. *"Once the diagnosis is made, the family no longer feel alone and can give a name to the illness that their child suffers from. It is also the first step towards research for therapeutic solutions and progress for genetic counseling".*

The teams at *Imagine* have already identified several hundreds of genes since the Institute was established. In 2018, their knowledge and their talents were again mobilized to continue advancing research.

They achieved major advances in many aspects of genetic diseases. Their work gave rise to 860 scientific publications in national and international journals.



New genes and mechanisms identified

The teams of **Prof. Jean-Laurent Casanova and Dr. Laurent Abel** of the *Imagine* Institute and Rockefeller Institute in New-York, are working on the **human genetics of infectious diseases and the immune response to infections.**

Through their work, they have identified a partial dysfunction of the DBR1 gene disrupting **defenses against common viruses** such as flu, HSV-1 and norovirus, which could then lead to a severe infection of the brain stem such as viral encephalitis (*Cell*, February 2018).

In 2018, researchers also outlined the involvement of a new gene, ZNF341, in **Hyper-IgE Syndrome (HIES)**, a genetic disease of the immune system which notably leads to a vulnerability to fungal and bacterial infections, and could also be the cause of severe allergies (*Science Immunology*, June 2018).

The team discovered a **genetic cause of the Whipple disease**, a chronic intestinal pathology, by noticing that the mutation of the IRF4 gene causes a deficiency of the immune response to the bacteria, Tropheryma whipplei, at the origin of the disease (*eLife*, March 2018).

It also highlighted a **molecular mechanism that reduces immunity to ß-papillomavirus** in patients with epidermodysplasia verruciformis. In these patients, deficiency of one of the proteins EVER1, EVER2 or CIB1 can allow the virus to cause a pathology (*Journal of Experimental Medicine*, August 2018).

WHEN THE STUDY OF A COMMON DISEASE PROVIDES KEYS TO UNDERSTANDING A RARE PATHOLOGY

The teams of Prof. Jean-Laurent Casanova and Dr. Laurent Abel have highlighted a mechanism that could cause vulnerability to tuberculosis, an infectious disease that affects more than 10.4 million patients worldwide. By blocking signaling pathways involving interleukins IL-12 and IL-13, the alteration of both copies of the TYK2 gene increases the risk of developing the disease after exposure to the mycobacteria Mycobacterium tuberculosis.

Through exploring this pathway, researchers discovered that a deficiency of these same interleukins could also be responsible for Mendelian susceptibility to mycobacterial disease (MSMD) syndrome, a group of rare genetic diseases characterized by infections from mycobacteria in tap water or BCG vaccines, for instance.

Science Immunology, December 2018

Dis cove ring

Since 2014, the Institute has approved four laboratories established at Hôpital Necker-Enfants malades AP-HP to advance research on joint projects and groups of specific diseases.

Among them, the laboratory of **Prof. Michel Polak** at Hôpital Necker-Enfants malades, **pediatric diabetology, endocrinology and gynecology** specialist. He identified TUBB1 as a new gene responsible for **congenital hypothyroidism**, which affects 1 child in 3,000 and is the most common endocrine genetic disease at birth. This gene was already known for its involvement in diseases associated with platelets and tubulin code constituent of microtubules located in the cytoplasm. The link between microtubules and platelets will be subject to in-depth research following this advance (*EMBO Molecular Medicine*, November 2018).

The teams of **Prof. Nathalie Boddaert** and her **multimodal brain imaging** laboratory, helps teams to speed up diagnosis through leading-edge imaging techniques.

Collaborate at the highest level

To advance research faster and have a better understanding of diseases, *Imagine* collaborates with teams all over the world, analyzing cohorts of patients on an international scale.

Within this scope, the laboratory of **Gaël Ménasché,** in collaboration with international teams, discovered a key molecule in immune system regulation. The team showed that when the TIM-3 protein is deleted or inactive following mutations of the HAVCR2 gene, the immune system stops functioning and T lymphocytes are overactive, resulting in a rare form of lymphoma, subcutaneous panniculitis-like T-cell lymphoma (SPTCL). This work leads to the reconsideration of this entity as an inflammatory disease rather than malignancy and to favor the use of immunosuppressants in its treatment (*Nature Genetics*, October 2018).

A BIOMARKER TO IDENTIFY RARE IMMUNE SYSTEM ABNORMALITIES

Genetic diagnosis, putting a name to the disease, helps understand the pathology and guide the therapeutic monitoring of apatient. It is essential for patients suffering from cancer as for some immunocompromised children, particularly for people with ataxia telangiectasia, a rare immunodeficiency disease.

This stage, which is still long and complex, should speed up thanks to the invention of the PROMIDISα biomarker by the teams of Patrick Revy and Jean-Pierre de Villartay. This biomarker uses 9 parameters to show very specific signatures of primary immunodeficiencies linked to V(D)J recombination defects or DNA repair.

Thanks to a collaboration with doctors at Hôpital Necker-Enfants malades AP-HP, Hôpital Robert-Debré, Hôpital Saint-Louis, and Institut Curie, the resort to PROMIDISα has already guided or confirmed the molecular diagnosis of patients. Researchers intend to promote its use as an addition to neonatal screening for severe combined immunodeficiencies.

Journal of Allergy and Clinical Immunology, June 2018

A EUROPEAN STUDY TO DIAGNOSE CHRONIC INFLAMMATORY BOWEL DISEASES

Symptoms such as chronic diarrhea, colitis and other lesions dangerously affect the life of patients with a chronic inflammatory bowel disease. In many cases, the genetic cause remains undetermined. However, the genetic diagnosis can be crucial.

The laboratory of intestinal immunity led by Nadine Cerf-Bensussan at the *Imagine* Institute launched a study, which compares the efficiency of diagnosis methods in partnership with the pediatric gastroenterology department of the Hôpital Necker-Enfants malades AP-HP.

The results of this study performed on the largest European cohort of this type showed that the arrival of the gene panel is a great advance. This technique has already benefited patients for whom the diagnosis has (re)directed therapeutic monitoring. For the purpose of better controlling patients' symptoms, the teams have already succeeded in rectifying some diagnoses.

Dis cove ring

There are also many advances in terms of neurodevelopmental disorders. For example, the teams of **Dr. Vincent Cantagrel and Laurence Colleaux**, who study **neurodevelopmental disorders**, revealed a new mechanism that makes the brain vulnerable to CDG syndromes (congenital disorder of glycosylation). Patients with CDG are more severely affected by a deficiency of a family of proteins that are vital for brain development, IgSF-CAM. This advance will allow us to better understand how some forms of neurodevelopmental disorders function (*eLife*, October 2018).

The strength of research at *Imagine:* translational research

Unique center for care and research on genetic diseases in Europe, *Imagine* brings together a continuum of expertise and a variety of fields of research from fundamental to applicative. The teams work in synergy on common and additional subjects, always in connection with clinical research and medical teams. It is this spirit at the Institute that allows research to advance more quickly.

"The spirit of excellence, the cross-disciplinary and collaborative environment, and cross-sectoral research that define Imagine make it possible to move faster for the benefit of patients. I have the opportunity to take part in major cross-disciplinary projects involving teams at the Institute, on campus and in Europe as well as industrial partners"

Antonio Rausell

Several multidisciplinary research programs launched in 2017 were developed in 2018:

- the DEVO-Decode program to explore non-coding DNA, coordinated by Prof. Stanislas Lyonnet and funded by the Fondation MSD AVENIR;
- the custom-made Dior Chair of tailored Medicine combining the expertise of Dr. Antonio Rausell and Prof. Marina Cavazzana to invent the medicine and personalized gene therapy of tomorrow;
- the RHU C'IL LICO "Medicine of the future for ciliopathies with renal failure", led by Sophie Saunier, Antonio Rausell, Nicolas Garcelon, Anita Burgun, and Stanislas Lyonnet, funded by the ANR as part of the French Investments for the Future program;
- DIM (Area of Major Interest) "Gene Therapy", supported by the Ile-de-France (Greater Paris) region, coordinated by *Imagine* and Prof. Marina Cavazzana, aiming to accelerate the development of gene therapy.

Dis cove ring

“After eight years of research abroad and in New York, I was looking for an environment in which I could set up a very ambitious research project. Imagine was one of the first institutes in France that was interested in this project and was able to offer me opportunities for collaborations and the required synergies.”

Mickaël Ménager,director of the ATIP-avenir Inserm team at the Imagine Institute, works on the combination of “machine learning” techniques and cell to cell gene expression analysis.

Five projects were developed as part of the Cross-lab program, which aims to promote cross-disciplinarity and have a leverage effect needed to raise major national or European public funding. Within this scope:

- The research teams of Gaël Ménasché, Mickaël Ménager, Frédéric Rieux-Laucat, Sylvain Latour, Antonio Rausell and Nicolas Garcelon study hemophagocytic lymphohistocytosis and the single cell;
- The research and clinical teams of Nadia Bahi-Buisson, Alessandra Pierani, Corinne Antignac, Vincent Cantagrel, Edor Kabashi, Jean-Pierre de Villartay, and the IPS platform of Nathalie Lefort work on developmental and pathological cell death in fetal and postnatal microcephaly;
- The data science platform teams of Nicolas Garcelon, with Vincent Benoit and Hassan Faour, the research and clinical teams of Marlène Rio, Jeanne Amiel, Valérie Cormier-Daire, Vincent Cantagrel, the medical data processing departments (Antoine Neuraz et Anita Burgun), of cytogenetics (Valérie Malan) and molecular genetics (Giuilia Barcia) of the Hôpital Necker-Enfants malades AP-HP are dedicated to the application of artificial intelligence in dysmorphology;
- The research teams of Frédéric Rieux-Laucat and Agnès Rötig, the reference centers of Brigitte Bader-Meunier, Pierre Quartier known as Maire and Arnold Munnich, are studying mitochondrial DNA maintenance defects and dysregulation of the immune response;
- The research teams of Jean-Laurent Casanova, Anne Puel, Laurent Abel and Alain Hovnanian are working on human inborn errors of keratinocyte-leukocyte interaction.

KEY FIGURES FOR RESEARCH AT *IMAGINE*

6

INTEGRATED CARE AND RESEARCH PROGRAMS (iCARPs)

28

RESEARCH TEAMS, INCLUDING 4 PARTNER LABS

15

CORE FACILITIES

5

ERC (EUROPEAN RESEARCH COUNCIL GRANTS)

860

SCIENTIFIC PUBLICATIONS WITHIN THE SCOPE OF IHU, INCLUDING 18 WITH IMPACT FACTOR (IF) ABOVE 30, 16 WITH IF BETWEEN 20 AND 30, 89 WITH IF BETWEEN 10 AND 20.

Core facilities supporting excellence in research

The research teams at the Institute benefit from the expertise of 15 core facilities involving all stages of research and the visualization of data to interpret them.

Imagine funds six of them in full and contributes to the funding of nine others, managed by SFR Necker. This structure unites *Imagine* Institute, the core facilities of the *Imagine* Institute and Necker-Enfants malades Institute INEM, and nine hospital units. In 2018, its management evolved.

In 2018, the management was entrusted to Dr. Fabiola Terzi and Prof. Isabelle André, in place of Claude-Agnès Reynaud and Prof. Nadine Cerf-Bensussan, who were commended for the quality of the term at this occasion.

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Developing today's best science for tomorrow's best medicine.

> Imagine *is an outstanding place because it aims to fulfil a dream to integrate research, care and teaching activities, to be as effective as possible and advance medicine, all to boost best medical research as much as possible.*

Prof. Alain Fischer, first Director and founder of Imagine Institute

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Identifying an altered gene is essential in the continued research to better understand the disease. Researchers can then explore the cellular mechanisms involved and above all try to restore them. This is the principle that prevailed in the creation of Imagine: synergize the expertise of doctors and researchers in one place to advance research on genetic diseases and cure them.

Since the creation of *Imagine*, discoveries are being made. In 2018, thanks to the molecular scissors, the famous CRISPR-Cas9, Annarita Miccio's laboratory succeeded in reactivating a gene that could improve the appearance of red blood cells in patients with hemoglobinopathies such as sickle cell disease and beta-thalassemia. Researchers reinitiate globin β production - when it is meant to be blocked after the fetal development stage - at sufficient levels to be considered in therapeutic protocol in the future (*Blood*, March 2018).

Céline Colnot's laboratory highlighted a new bone repair strategy following the discovery of stem cells within the periosteum, the tissue covering the outer surface of bones. The high regenerative potential of these cells provide a new and interesting therapeutic strategy in the treatment of bone repair defects (*Nat. Commun.*, February 2018).

"When we arrived at Imagine Institute, what changed is that we were listened to. We found ourselves in front of doctors who understood the situation (...) and people who were genuinely interested in our case." Maureen

"Today we hope to be able to better diagnose the pathology so that we may launch the 2nd stage in the search for treatment" Dimitri

Maureen and Dimitri are the parents of Lila, 5 years old who suffers from a rare autoinflammatory disease.

Understanding altered mechanisms in genetic diseases is an essential stage in developing treatments. All of the 24 research teams and 4 partner labs therefore work closely with the clinicians at Hôpital Necker-Enfants malades AP-HP to explore all diseases and better understand them.

Neurodevelopmental genetics is strengthened at *Imagine*

In 2018, after being selected by the Scientific Advisory Board in 2017, Edor Kabashi's research team strengthened the Institute's neurobiological competence. His translational research team on neurobiological disorders aims to identify new genetic causes of amyotrophic lateral sclerosis (ALS) and epilepsy, and develop mutant zebrafish models, carriers of the same mutations, to study neurodegenerative processes. They join many doctors and researchers at the Institute who are already working on a better understanding of neurodevelopmental diseases.

"We are trying to identify new genetic interactions by analyzing cohorts of patients with these diseases. Through cellular and animal models, we are trying to understand the pathophysiological signature of the diseases and to detect neuroprotective factors which will be used in clinical trials. We hope that we can develop treatments for some of the neurological problems."

Edor Kabashi
Director of a new research team

ALL RESOURCES ARE GOOD! REPOSITIONING A MOLECULE TO TREAT A GENETIC DISEASE THROUGH ANTI-HIV DRUGS

Naturally, better knowledge of a disease can lead to the development of targeted treatments, but also to the unexpected use of previously discovered molecules, initially intended for a different use.

This was the case for Aicardi–Goutières syndrome, a rare genetic disease causing severe neurological problems. The disease is associated with an overproduction of interferons α, for which the toxicity in brain cells is unknown. The study of this pathology has highlighted strong similarities with the "reverse transcription" activity of the HIV-AIDS retrovirus. Also in 2018, a study driven by a team at Hôpital Necker-Enfants malades AP-HP and the AP-HP clinical investigation center, and the neurogenetics and neuroinflammation laboratory of Yannick Crow at *Imagine* Institute showed that an antiretroviral treatment, initially intended to fight HIV-AIDS, reduced specific biological perturbations observed in Aicardi-Goutières syndrome for the first time.

(*N Engl J Med.* Dec 2018)

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Research and clinical combination

In 2018, a 4th partner lab, led by Prof. Yves Ville, surgeon and obstetrician at Hôpital Necker-Enfants malades AP-HP, who operates in utero on fetuses with serious malformations, joined his strengths with those of other teams at *Imagine*. This multidisciplinary team focuses on the development of in utero therapies for children with congenital malformations or infected with cytomegalovirus (CMV). With the laboratory Impact@*Imagine*, Prof. Yves Ville intends to study a multidisciplinary and innovative prenatal approach to congenital anomalies and their treatments.

"Our research work aims to improve the prenatal care of patients presenting with congenital anomalies. In particular, we work on in utero surgery for fetal malformations, fetal CMV infection treatment, fetal phenotyping by ultrasound or MRI, and artificial intelligence in prenatal diagnosis."

Yves Ville
Director of a new research team

Leading-edge core facilities serving the excellence of researchers and the care-research continuum

In the same way, the 15 core facilities now at the *Imagine* Institute, are a key lever in medical research and advances. They ensure that doctors and researchers have access to leading-edge technology, combined with high-quality human expertise. In 2018, a new core facility was established. Put under the responsibility of Marcelo Simon Sola, the rAAV platform aims to develop new vectors essential to gene therapy. This treatment (see box page 31) consists in repairing defective genes by introducing the healthy gene to the heart of the cells. This technology requires "carriers" with highly specific characteristics. Therefore, the purpose of the platform is to produce such vectors not only for *Imagine* teams studying this therapeutic approach, but for all DIM (Area of Major Interest in Ile-de-France) gene therapy teams coordinated by Marina Cavazzana at *Imagine* Institute. In addition, the genomics platform managed by Christine Bole-Feysot at the *Imagine* Institute took part in the medical first of Dr. Guillaume Canaud (Institut Necker-Enfants malades) and the teams of Hôpital Necker-Enfants malades, AP-HP, Université Paris Descartes and Inserm. Patients previously identified as carriers of the gene involved in CLOVES syndrome by the genomics platform benefited from the new treatment developed by Guillaume Canaud's team, and the impressive results observed in malformation regression.

WORLD FIRST FOR GENE THERAPY IN BETA-THALASSEMIA

After the 2017 success in patients with sickle cell disease, it is time for another form of severe anemia, beta-thalassemia, to benefit from gene therapy. This common monogenic genetic disease affects nearly 288,000 people worldwide with 60,000 new cases per year. As part of an international multicenter trial coordinated by Prof. Marina Cavazzana (AP-HP/Inserm/Université Paris Descartes) and her teams at Hôpital Necker-Enfants malades AP-HP, gene therapy was offered to 22 patients in France, USA, Thailand and Australia. The patients treated in this trial now produce a therapeutic hemoglobin in sufficient quantities to stop the need for monthly blood transfusions. This treatment consists in replacing the "sick" gene with a healthy gene: first, bone marrow stem cells, cells able to create all cell lines present in the blood, are taken. Before reinjecting them into the patient, a functional gene is introduced into these cells to compensate for the altered gene. The life of these patients has already changed significantly.

"I'm nearly 24 years old, I had an autograft 4 years ago. Thanks to that, today, I no longer need transfusions but above all no more Desferal, which was my treatment in the form of subcutaneous injections that I had to do every day to lower my ferritin. It was quite complicated, especially mentally because I was young and I didn't feel like the others [...] I am happy I had the opportunity to have this autograft and I want the same for all patients."

Testimony of a patient with beta-thalassemia treated with gene therapy.

Making every effort so new therapies are created

To make more discoveries available, the *Imagine* Institute gives resources to clinical research teams and deploys clinical research programs. Clinical research is a crucial stage in the development of new diagnostic and therapeutic approaches improving patient care.

The clinical research department managed by Salma Kotti is focused on the reference centers for rare diseases andclinical departments that make up the clinical scope of *Imagine*. The sponsorship team is made up of project managers and a clinical research officer. The investigation team is made up of clinical research coordinators, clinical study technicians and nurses. In 2018, a 3rd mobile clinical research nurse, Léa Peroni, and two clinical study technicians, Narimene de Nadaï and Marc Melesan, strengthened the team.

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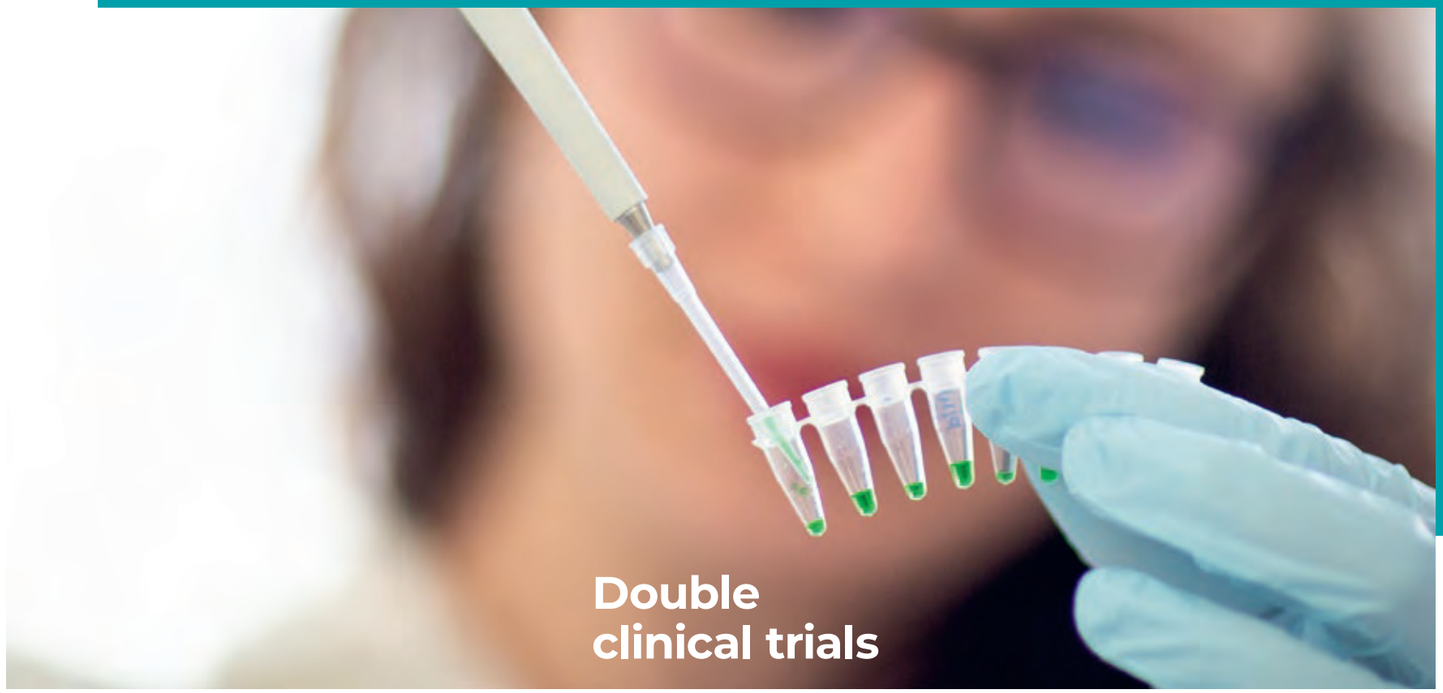


Double clinical trials

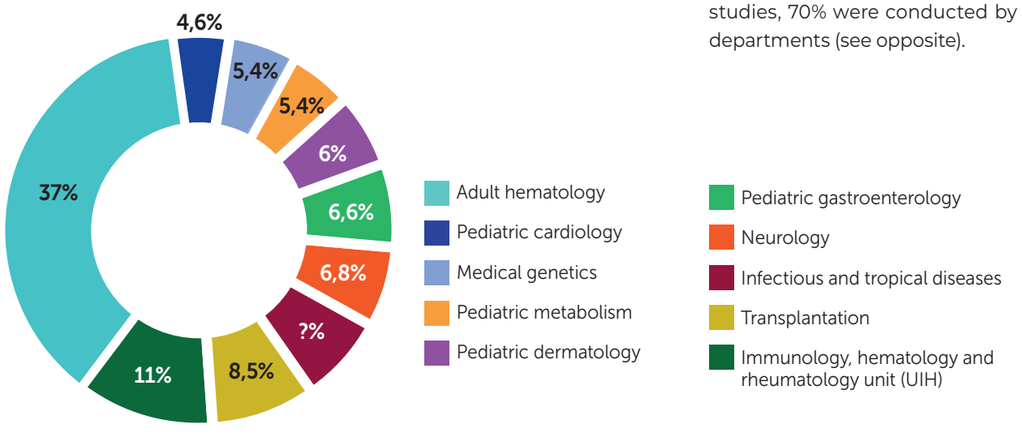
"Our objective is to facilitate the implementation of clinical trials and studies within the field of innovation at Imagine *for the researchers and clinicians of our founding members, APHP, Inserm and Université Paris Descartes",* Salma Kotti explains. *"We support them throughout the entire project cycle".* At an earlier stage, the coordinators of clinical research intervene to consider the feasibility of the study with the trial investigators. In 2018, 15 reference centers out of 25 (see diagram pages 34-35) benefited from this valuable assistance in investigation to implement and start studies, help select patients and therefore increase the number of enrollments and manage the clinical trials on a daily basis. These studies are managed either directly by the investigation team or in support of the Mother-Child Clinical Investigation Center (CIC) at Hopital Necker-Enfants malades AP-HP.

Mobile clinical research nurses play a key role in the care of patients taking part in clinical trials.

Now with 3, they take samples essential to the trial, and provide a connection between the medical teams and trial sponsors. In 2018, the implementation processes of clinical studies with AP-HP or Inserm sponsorship were also defined, with the Clinical Research and Innovation Division (DRCI) and CIC/URC of AP-HP, and the clinical research center of Inserm. This "IHU Track" project was created and developed in 2018 to accelerate the sponsorship of clinical trials by our founding members. At the time of writing this report, two project managers were recruited.

In 2018, 580 clinical studies enrolling more than 7,000 patients were underway within the clinical scope of IHU *Imagine*, involving the reference centers for rare diseases, the clinical departments at Hôpital Necker-Enfants malades AP-HP, and two clinical investigation centers. Out of these studies, 70% were conducted by 10 clinical departments (see opposite).

10 main clinical departments that conducted clinical trials in 2018



Half of the studies relate to research on a drug, medical device, cellular or gene therapy, and nearly 50% are phase III clinical trials, the stage where their effectiveness is tested. Sponsors of these studies are either industrial (41.5%), or institutional (58.5%). Clinical research coordinators and clinical research technicians at *Imagine* took part in 71 studies and enrolled 1,260 patients. Mobile clinical research nurses were mobilized for 44% of studies (730 enrollments).

In the coming years, *Imagine* is focused on the goal of doubling the number of clinical trials within the reference centers for rare diseases to eventually double the therapeutic solutions. Today, 52 therapeutic solutions are being tested in the labs at *Imagine*, in the pre-clinical or clinical stages, providing hope that they will be successfully concluded in the next 5 to 10 years for the benefit of more than 100 rare diseases and 50,000 children in France, targeted by these solutions. To reach this ambitious goal, *Imagine* has entrusted the mission to Prof. Marina Cavazzana, Director of the Department of Biotherapy and Biotherapy Clinical Investigation Center at Hôpital Necker-Enfants malades AP-HP, and co-director of the Inserm Human Lymphohematopoiesis Lab at *Imagine*, and Jean-Marc Tréluyer, CIC Director at Hôpital Necker-Enfants malades AP-HP, one of the leading programs of its 2028 strategic mission, the one on clinical research.

REFERENCE CENTERS FOR RARE DISEASES: THE HEART OF THE CARE

Rare diseases include 9,000 different pathologies and 3 million people affected in France alone. They are serious, chronic and disabling diseases affecting all organs and expressing themselves in different ways. They require specialist, burdensome and long-term care, so reference centers were created to structure the supply of health services for patients and provide optimum care on every part of it. Reference centers facilitate patient diagnosis and care, coordinate research work, improve the understanding of pathologies for patients and are key contacts for patient associations.

A total of 25 reference centers for rare diseases at Hôpital Necker-Enfants malades AP-HP are now affiliated with the *Imagine* Institute. In July 2018, 10 new reference centers for rare diseases (RCRD) have chosen to be connected with *Imagine* Institute (see box pages 34-35).

"These centers, organized around highly specialized teams, facilitate patient care and supply health services in connection with all health professionals concerned" commented Laure Boquet, General Delegate of* Imagine. *"They are key contacts for patient associations and families, and play a significant role in the development of clinical trials".

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25 reference centers for rare diseases affiliated with *Imagine*

Intellectual disabilities of rare causes | Marlène Rio

DI - RETT center
| Nadia Bahi-Buisson

CRéER - Rare epilepsies
| Rima Nabbout

Pediatric hemophilia
| Annie Harroche

Major sickle cell syndromes
| Marianne de Montalembert

Mastocytosis
| Olivier Hermine

CEREDIH - Hereditary immunodeficiencies
| Alain Fischer

RAISE - Juvenile arthritis
| Pierre Quartier Dit Maire

MARDI - Rare digestive tract diseases
| Olivier Goulet

MARHEA - Hereditary kidney diseases of the child and the adult
| Rémi Salomon

MALO - Rare ENT malformations
| Françoise Denoyelle

Genetic deafness
| Sandrine Marlin

OPHTARA - Rare ophthalmological diseases
| Dominique Brémond-Gignac

MAGEC - Genetic diseases with cutaneous expression
| Christine Bodemer

Developmental abnormalities and malformation syndromes in the Ile-de-France (Greater Paris) region | Jeanne Amiel

M3C - Complex congenital Heart Defects
| Damien Bonnet

MOC - Constitutional bone diseases
| Valérie Cormier-Daire

Pierre Robin sequence and sucking and swallowing congenital disorders
| Véronique Abadie

MAFACE - Cranial and facial malformations | Arnaud Picard

Craniosynostosis and craniofacial malformations
| Michel Zérah

Rares Vertebral and spinal malformations
| Michel Zérah

MAReP - Rare anorectal and pelvic anomalies
| Sabine Sarnacki

Rare gynecological pathologies
| Michel Polak

MAMEA - Hereditary metabolic diseases
| Pascale de Lonlay

CARAMMEL - Mitochondrial diseases
| Arnold Munnich

10 NEW REFERENCE CENTERS FOR RARE DISEASES IN 2018
(in blue in the graphs)

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Dr. Warehouse: artificial intelligence to shape the medicine of tomorrow

Dr. Nicolas Garcelon's team developed Dr. Warehouse, a free software intended for doctors, which, through text analysis for and by doctors, puts together cohorts for clinical studies, obtains the phenotypical description of a population, analyzes the medial journey of patients and their families, and therefore improves knowledge of rare diseases, reduces the diagnostic odyssey of patients and helps with their care. Used since January, 2017 at Hôpital Necker-Enfants malades AP-HP, this software, which prefigures the personalized medicine of tomorrow, is now offered in opensource.

With Dr. Warehouse, doctors have the ability to find and enroll patients for clinical research. In the same way as Google, doctors type one or several words into a search bar, then the system gives them a selection of patients who present with these distinctive characteristics and related texts. In this way, they can explore data for feasibility studies, create cohorts of patients, save searches and receive alerts when a new patient meets their search criteria.

"The progress made by using data benefits both undiagnosed patients but also, more generally, all patients with a specific clinical profile. At the end of 2018, the database already contained 680,000 patients, 5.6 million documents, 50 million structured data items, and 600 cohorts of patients. Fully configurable data, which correspond to ethical criteria", Nicolas Garcelon explains.

Favoring translational research, when a new mutation is detected Dr. Warehouse finds similar patients to see if they are carriers of it or accesses the diagnosis by finding patients similar to an undiagnosed patient.

Journal of Biomedical Informatics, March 2018.

INNOVATION IN THERAPEUTICS: TECHNOLOGY TRANSFER

Protect, support, and transfer to benefit the largest number

Out of the 4 missions of *Imagine* is the transformation of researchers' advances in innovations for the benefit of patients and the Institute in general. Technology transfer therefore accelerates progress from the laboratory to the patient's bedside. This progress from proof of concept to a diagnostic test or therapeutic strategy can only happen in close collaboration with industrial partners.

As soon as a discovery is eligible to become a possible innovation, it must be protected with a patent. In 2018, 9 new patents were filed. *Imagine*'s patent portfolio covers an extensive range of fields and therefore amounts to **41 active patent families** from *Imagine*'s labs activities and **5 operating licenses** that are signed or in the process of being finalized. For most of them, the search for industrial partners continues. It is an essential stage so that the development, production and marketing of innovation may take place. It can become a reality in various ways: research collaboration with licensing option, grant of license or even creation of a start-up. 15 new R&D partnership agreements or amendments were signed - including 2 contracts directly from the highly selective "Sanofi Awards" program - helping to fund laboratory research projects. All industrial contracts in force in 2018 managed by the *Imagine* Foundation generated **€4 million** in annual takings, most of which was put back into research projects.

Building momentum for innovative projects

2018 saw in particular the rapid expansion of cross-disciplinary projects, the optimization of interactions with technology transfer and clinical research structures of founding members, and the development of *Imagine*'s unique ecosystem regarding innovation and value creation.

In 2018, **4 new cross-disciplinary projects** were initiated as part of the Cross-lab internal funding program, involving 14 laboratories, 7 reference centers and 3 core facilities.

One project in the field of autoimmune and inflammatory diseases based on **Single-cell analysis approaches**, led by Prof. Frédéric Rieux-Laucat, was set up in response to the RHU4 call for projects, placing *Imagine* at the center of a large consortium bringing together Inserm, AP-HP, Institut Pasteur, Institut Curie, INRA, CEA, and the companies Sanofi and Ariana Pharma. This highly ambitious project, comes within the scope of the continuation of the first project supported by the Cross-lab program in 2017.

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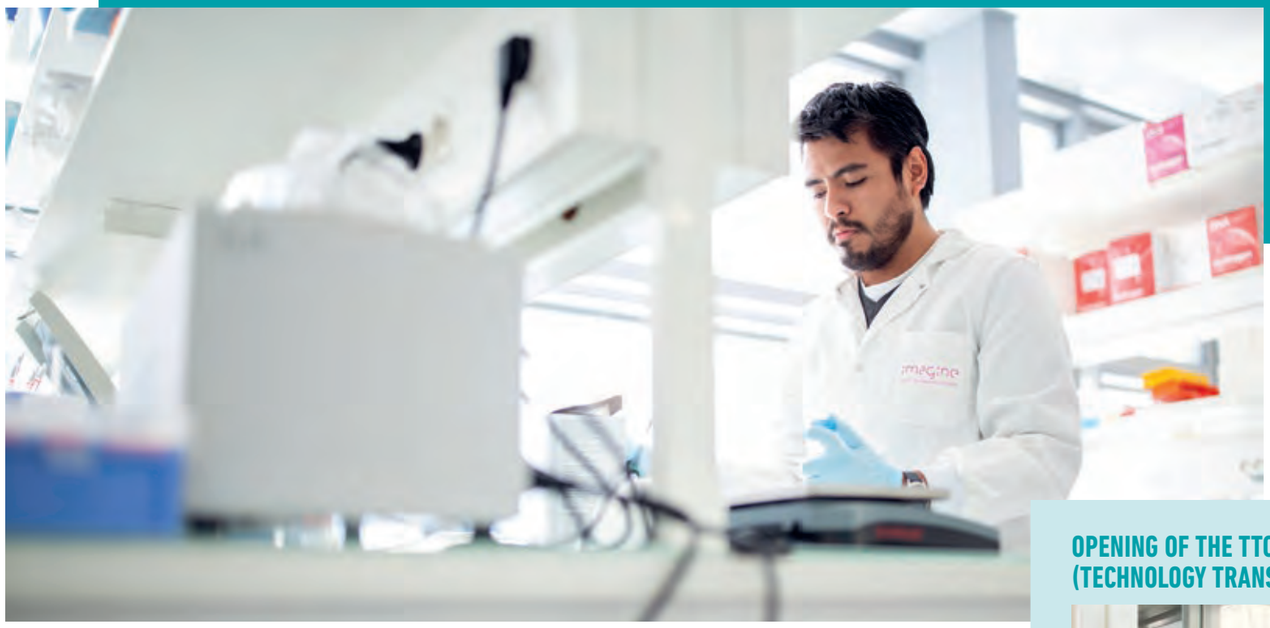


DIM gene therapy, supported by the Ile-de-France (Greater Paris) region, initiated 10 new projects on a regional scale. Among the projects in line with the DIM gene therapy guidelines, a project in the field of sickle cell disease, led by Annarita Miccio, was subject to Innograft funding, resulting in a patent being filed. This program, initiated in 2017 by *Imagine* Institute, gives funding to a team for 12 months to facilitate progress from discovery to proof of concept. *"It is usually the difficult stage for researchers"*, comments Romain Marlange, Director of the Innovation and Technology Transfer Department. *"This boost should help start projects with a view to an industrial partnership or creation of a start-up."*

Finally, 2018 also saw the continuation of the DEVO-Decode project funded by MSDAVENIR, involving 8 laboratories, 8 reference centers and 8 core facilities, and the start of the C'IL-LICO project, winner of the RHU3 call for projects in 2017.

The Bioentrepreneurs program, set up jointly in 2016 with Université Paris Descartes, the Ecole polytechnique and HEC Paris, welcomed its 3rd class of students in 2018, made up of 9 students working on 5 new healthtech projects from *Imagine* and other research institutes.

Finally, 2018 saw the in-depth investigation of the Springboard project, the first funding and expertise accelerator fully dedicated to genetic diseases. This project should emerge in the second half of 2019: by associating all the necessary experts including industrial and entrepreneurial, it will help support leading projects at *Imagine* with a high potential to develop diagnostic or therapeutic solutions and particularly intended for a start-up creation.

OPENING OF THE TTO@*IMAGINE* SPACE (TECHNOLOGY TRANSFER OFFICE)

In 2018, new Innovation and Technology transfer collaborative work spaces dedicated to technology transfer, clinical research, grant office and legal department teams, and the technology transfer structures of our founding members were created by *Imagine*'s top management.

"*This space contributes to the inclusive organization set up in 2016 with the technology transfer structures of the founding members (Inserm Transfert, AP-HP/OTTPI and SATT Idfinnov). The aim is to bring together advocates of the research teams but also advocates between themselves to accelerate the rollout of partnership and technology transfer projects*" explains Romain Marlange, Director of the Innovation and Technology Transfer Department at the *Imagine* Institute.

As shown by one of the "users" of TTO@*Imagine*, Matthieu Collin, Director of Intellectual Property at Inserm Transfert: "*We are delighted to partner up with this innovative approach, which is a first in an institute of research. Direct exchanges, sharing information and the proximity between teams from different structures are a huge bonus and will contribute to accelerating projects.*"

Developing the technology transfer ecosystem at *Imagine*

Imagine is integrated into a dynamic ecosystem, conducive to the development of biomedical innovations. Partner of the consortium Findmed (bringing together the Carnot Institutes in the field of health and chemistry), member of the Medicen Paris Region competitiveness cluster, *Imagine* is also a privileged partner of the consortium Human Health Start-up Factory, coordinated by Inserm Transfert and winner of the French Tech Seed call for projects in 2018. This partnership helps *Imagine* to guide the most promising start-ups from their research activities to a system of mentoring and pre-seed funding by Bpifrance.

Imagine also signed a hosting and partnership agreement with France Biotech in 2018, the association of entrepreneurs in health innovation, the purpose of which is to facilitate health innovation in France and help start-ups and SMEs in this sector to become successful companies, capable of quickly conceiving new therapeutic solutions.

"The France Biotech association is glad to set up its offices at the Imagine Institute, a leading medical research center both nationally and internationally. This geographical proximity is a strong indication of the obvious and undeniable synergies between the worlds of public medical research and that of start-ups, whether it is on the subject of technology transfer or clinical trials, to develop the therapeutic solutions of tomorrow for the benefit of patients" said Maryvonne Hiance, President of France Biotech.

"The installation of France Biotech at Imagine is fully in line with the Institute's ecosystem movement, approved as Tremplin Carnot in 2016. It will contribute to increasing partnership opportunities or creating businesses, as well as opening up professional opportunities to our community of researchers", stated Stanislas Lyonnet, Director of *Imagine* Institute.

Opening up

Be an active player in society.

Imagine's universal goal,
that of changing the lives of countless
patients the world over,
is disseminated, shared and talked
about beyond its boundaries,
to its campus, to talents
in France and internationally,
and to world science.

Prof. Arnold Munnich, President of the Imagine Foundation

Opening up

Sharing knowledge and discoveries with the scientific and medical community, young talents and the general public is a vital mission for the Institute. Since its creation, *Imagine* has been committed to offering its members real life at the Institute and endeavors to share, learn and raise awareness, always in an open and cross-disciplinarian spirit, with a focus on international influence.

Imagine's top priorities: education and training

Through the training of future doctors and researchers and continuous training of doctors and health professionals, the *Imagine* Institute promotes expertise in both research and medicine, which makes it unique. This mission is carried out with Université Paris Descartes, founding member of *Imagine*, and its doctoral schools, and could not develop without the loyal and generous support from the Fondation Bettencourt Schueller.

FONDATION BETTENCOURT SCHUELLER

For over 30 years, the Fondation Bettencourt Schueller has chosen to "Give wings to talent" to contribute to the success and influence of France. In addition to funding the "Liliane Bettencourt Chair of Developmental Biology" managed at *Imagine* by Dr. Matias Simons, the Foundation, which has been an honorary patron of *Imagine* Institute since 2012, has contributed significantly to the Institute's educational mission. It provides support to the Institute's conference center, which helps to disseminate knowledge through organizing conferences and scientific discussions, and it funds half of the training programs through and on research (MD-PhD, International PhD, Time for Research), as well as the *Imagine* Masters in Bioentrepreneurship co-founded by *Imagine*, Ecole Polytechnique, Université Paris Descartes and HEC Paris.

Programs to promote expertise in both research and medicine

In 2017-2018, the Fondation Bettencourt Schueller renewed the support that it has given for 4 years to train PhD students in science and young researchers. In 2018, 7 new awardees benefited from these programs, which is an invaluable help for the life of *Imagine*'s research laboratories.

Three doctors took advantage of the Health-Science MD-PhD program, which helps young doctors who have already achieved a Master's 2 in research to complete their training through research, by preparing a science thesis under the tutorship of one of the researchers in one of *Imagine*'s laboratories.

Paul Bastard

Study of a new susceptibility gene for herpes encephalitis in children: TMEFF1

Yasmine Benadjaoud

Molecular bases and genetic models of a congenital heart disease: a pilot study in congenital corrected transposition of large vessels and transposition of large vessels

Ségolène Bernheim

Role of Greb1l in left-right asymetric heart morphogenesis and congenital heart defects

On this program, Déborah Jorge Cordeiro, MD-PhD 2017-2018, enthusiastically recalls: *"A tremendous opportunity to conduct a research project within a dynamic Institute, where scientific collaborations as well as the facilities available allow for projects to progress quickly and effectively. The Institute's situation within Hôpital Necker-Enfants malades AP-HP and the ongoing interaction with clinicians and researchers from fields other than ours are essential drivers in our scientific advances in therapeutics."*

Three international students joined the *Imagine* research teams thanks to the International PhD program.

Panagiotis Antoniou

Genome editing approaches for the treatment of ß-hemoglobinopathies

Francisco Requena

Development of bioinformatics methods for the integrative analysis of high-dimensional multi-omics datasets in functional genomic

Victor Garcia

Understanding the molecular mechanisms of HIV-1 interactions with Dendritic cells

The goal of the *"Time for Research"* program is to bring together clinicians in clinical or fundamental research developed at *Imagine*, giving them *time* to conduct their research project. In 2018, a new clinician was selected for the program.

Pr Rima Nabbout

Developmental genetic epilepsies as model of multi-system excitability: a patient driven translational research, in Edor Kabashi's laboratory

According to Dr. Simane Allali, *"Time for Research"* since 2016: "*The exceptional environment that I have had the opportunity to enjoy at the Imagine Institute has helped me to fully focus on highly rewarding fundamental and translational research activities. Conversely, collaborations between teams have had a significant impact in my opinion, forging strong links between CMR Sickle cell disease and the Imagine Institute".*

Opening up

2nd and 3rd intakes of the *Imagine* Masters program in Bioentrepreneurship

Launched in 2016, the Bioentrepreneurship program by the *Imagine* Institute, Université Paris Descartes, HEC Paris and Ecole Polytechnique, helps students driven by the desire to work in the health industry to challenge their knowledge on the reality of creating an innovative company. The program focuses on innovative companies founded on real assets, experimental, technological or coming from an observation of real needs.

Students, future doctors, pharmacists, engineers or entrepreneurs, come to complete their academic journey here to get a cross-disciplinary perspective on biomedical entrepreneurship.

Supported by the Fondation Bettencourt Schueller, the program is led by Pr. Olivier Hermine, *Imagine* laboratory director and Head of the Adult Hematology department at Hôpital Necker-Enfants malades AP-HP.

This unique approach combines "learning by doing" and works in small groups with complementary skills to meet the needs of entrepreneurs in the world of science and hospitals, but also to those in healthtech, a fast-growing sector intersecting science, health, technology and business. 4 start-ups have been created or are in the process of being developed following this program.

Creating vocations with the youngest

Since 2013, *Imagine* has taken part in the Research Apprentices initiative, developed by Frédéric Rieux-Laucat, in partnership with the association Arbre des Connaissances.

Throughout the school year, the scientists at *Imagine* introduce students to the life of a laboratory, the world of research, and conduct a science project in pairs.

Following the example of the researchers, from their immersion, research apprentices presented their success on May 30, 2018 at *Imagine*, at the Research Apprentices' Conference.

"This project, which is completed with junior and senior high school students from neighboring establishments, is an opportunity for researchers at Imagine Institute. It helps us to establish a close link with young people, to introduce them to life sciences through research, and sometimes even reveal a vocation for these disciplines. The wealth of exchanges was in fact both a human as well as a scientific adventure", commented Frédéric Rieux-Laucat, Manager of the Research Apprentices program.

In 2018, the Institute also welcomed 40 interns from junior and senior high schools in Paris, Ile-de-France (Greater Paris) and beyond.

In addition to these training programs, the *Imagine* Institute is committed to providing its doctors, researchers and students with an attractive and stimulating research environment, open to both the campus and the world.

A space conducive to emulation

In 2018, *Imagine* implemented and developed actions aiming to promote the scientific and social life of the Institute, as well as a mindset focused on innovation and collaboration.

Therefore, laboratory directors and staff representatives from the Institute (researchers, PhD students and post-docs, engineers, technicians and admin staff) gathered together three times at the IHU Board of Management to discuss the main scientific guidelines and research resources.

Every month, researchers come together to talk about topics related to the Institute's social and scientific life and their laboratories during the "Café des chercheurs" [Researchers cafe].

The Young Researchers Association (YR2I) and the *Imagine* Sport Association organize different scientific, social and sporting events, which create connections and synergies between members of the Institute.

In September, laboratory directors and members of the Institute's management reflected and contributed to *Imagine*'s strategic and scientific prospects during an annual retreat of a few days.

Throughout the year, Institute members benefited from scientific seminars and conferences organized within the Institute's conference center. A place of scientific and associative activities, in 2018, it welcomed more than 40 scientific seminars, but also symposiums open to those outside the Institute, led by researchers, reference centers for rare diseases,rare diseases networks, patient associations or private companies. PhD thesis defenses of students at the Institute were also organized in the conference center.

Opening up

Supporting students and young researchers

28% of *Imagine* Institute members are students, PhD students or post-docs. *Imagine*'s priority is to offer the best welcome to its French and international young researchers and future doctors, to give high-quality training and help them to improve in the best conditions.

Created five years ago, the Young Researchers Association at *Imagine* (YR2I) is a key player in the scientific and social life of young researchers and plays a key role in generating synergies between scientists.

In 2018, the association organized 9 seminars, where young researchers presented their work in front of an audience of researchers, educators and their PhD supervisor. These monthly seminars facilitate stimulating interactions between established and up-and-coming researchers, with the latter benefiting from constructive criticism of their research efforts.

The YR2I association is also involved in inviting 2 internationally renowned researchers, from the various fields of genetics to the weekly *Imagine* seminars and to lunches where young and guest researchers may meet.

The association regularly organizes professional breakfasts for young researchers and takes part in the BIOTechno Science Forum.

4TH YOUNG RESEARCHERS CONGRESS AT THE *IMAGINE* INSTITUTE

On May 24, 2018, the 4th Young Researchers Congress was held at *Imagine*, a key event where PhD students, post-docs, engineers and technicians presented their work to the whole Institute using spoken and poster presentations. This event was a source of major discussion and collaborations, and the opportunity to identify the most innovative and promising projects.

The Congress in figures:
- 184 participants
- 15 spoken presentations in the *Imagine* auditorium
- 31 poster presentations

The Congress also welcomed professor Sylvain Chaty, Astrophysicist at Université Paris Diderot, who captivated the audience with his lecture "Search for life in the Universe".
"My first edition of the YR2I congress was an amazing experience! A standard of scientific excellence mixed with a very friendly atmosphere is in fact the perfect place for scientific discussion. I also had the opportunity to take part in the organization, as well as in the scientific committee for this event, both of which were highly rewarding."
Cyril Longé, member of the association in 2018 and current President

An Institute with an international scope

First center for research and care in genetic diseases in Europe, *Imagine* endeavors to attract talents from all over the world and influence advances and research on an international scale.

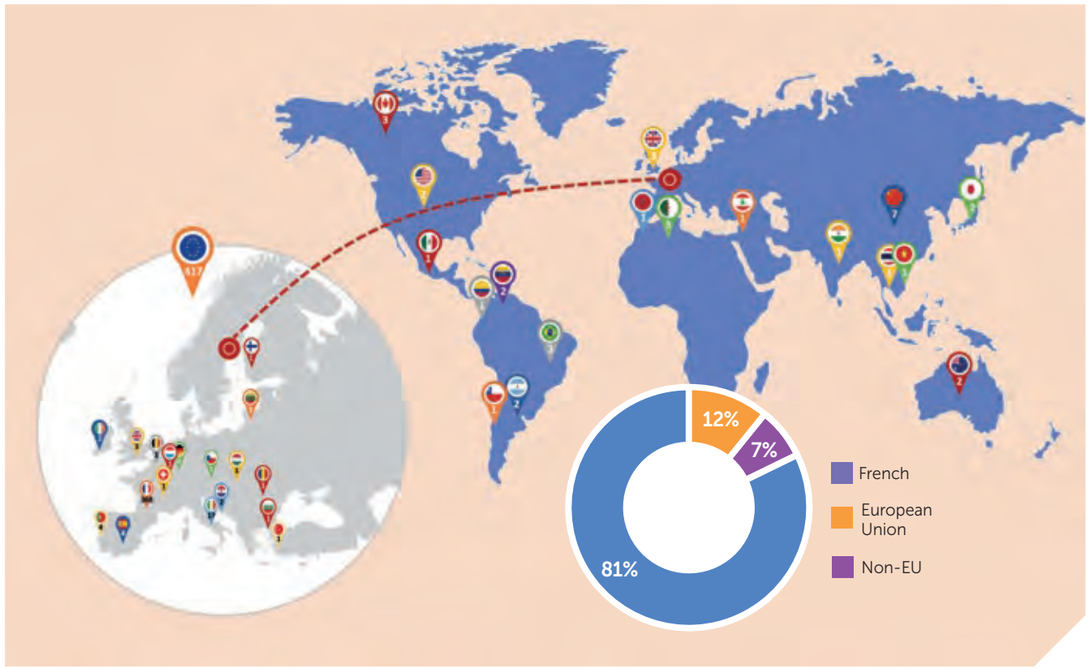
19% of *Imagine* Institute's members are of foreign nationality, coming from 35 countries to research excellence.

In October 2018, the scientific strategy and the recruitment of teams were redefined by *Imagine*'s Scientific Advisory Board, made up of prominent global scientists, and chaired by Prof. Elizabeth Blackburn, 2009 Nobel Prize in Medicine.

With the objective of developing a broader international scope, this year the Institute signed international collaboration agreements, and hosted visits from international universities, research centers and hospitals with a view to future collaborations.

A Memorandum of Understanding on future scientific and academic collaborations was signed with His Highness Prince Turki Bin Saud, President of King Abdulaziz City for Science and Technology in Saudi Arabia. A partnership was initiated with Hamad Bin Khalifa University (HBKU) in Qatar to identify common research topics and submit joint applications to calls for tenders. The Institute also signed a collaboration agreement for education programs with the Guangzhou Children's Hospital in China to welcome PhD students and post-docs.

Finally, out of 190 applications, two researchers at the Institute, Frédéric Rieux-Laucat and Mickaël Ménager, were selected and are among the 19 winners of the European academic partnership program "Sanofi iAwards Europe" for their research projects on monogenic diseases and immunomodulation (Frédéric Rieux-Laucat) and on the genomics of autoinflammatory diseases (Mickaël Ménager).



Opening up

Imagine has organized or taken part in a wide range of international conferences and courses.

In March, 2018, *Imagine* hosted on-site the first edition of the Eurodis Winter School on innovation and translational research. Throughout the year, members of the Institute are involved in many international conferences, such as the European Society of Human Genetics conference in June 2018. The Institute also hosted major international conferences such as the Henry Kunkel Society Congress in March 2018 and organized the first edition of the international conference on gene therapy, the Gene Therapy Partnering Day.

1ST INTERNATIONAL EVENT ON GENE THERAPY AT *IMAGINE*

On September 17th, 2018, the *Imagine* Institute organized the first Gene Therapy Partnering Day, in collaboration with Medicen Paris Region and the Île-de-France (Greater Paris) Region. Throughout this day of meetings between academic and industrial experts, the main European players in gene therapy were able to discuss the challenges raised by this future treatment, its new applications, its techniques, and its marketing.

In figures:
150 participants
20 presentations
More than 100 meetings/business meetings

Since 2017, gene therapy has been approved as an Area of major interest (DIM) by the Ile-de-France (Greater Paris) region. The goal of the DIM Gene Therapy project led by *Imagine*, and coordinated by Prof. Marina Cavazzana, is to accelerate therapeutic innovations and improve the care of patients with rare, common or even chronic diseases.

In 2018, within its conference center, the Institute hosted more than 40 conferences, scientific colloquia and symposia, during which researchers from *Imagine* laboratories, Hôpital Necker-Enfants malades AP-HP campus, and guest researchers from France and other countries shared their advances and discussed specific themes, always with a focus on accelerating discoveries and their application for the benefit of patients.

Getting involved in its own environment

The *Imagine* Institute continued its efforts to open and integrate, primarily on the Hôpital Necker-Enfants malades AP-HP campus, especially with the first year of approval of Prof. Yves Ville's laboratory, associated with *Imagine* Institute. The Institute secured 10 new reference centers for rare diseases, bringing the total to 25 in 2018.

This year, the *Imagine* Institute continued the rollout and development of DIM (Area of Major interest) gene therapy, spearheaded by the Ile-de-France (Greater Paris) region and Prof. Marina Cavazzana at *Imagine*, and the goal of which is to accelerate the development of gene therapy.

In 2018, the Institute was involved in the management and implementation of the 2025 French Plan for Genomic Medicine by taking part:

- in the management of the General Assemblies of the Paris Region very high-throughput genomic platform "SeqOIA". Led by AP-HP, Institut Curie, Gustave Roussy and *Imagine*, it aims to perform whole genome sequencing from all over the country;
- in the management of the "DEFIDIAG" project, which combines geneticists, epidemiologists, economists, sociologists and psychologists, and aims to study the feasibility and efficiency of using whole genome sequencing for etiological diagnosis of intellectual disability.

The *Imagine* Institute is involved in research beyond its scope with the medical community and patient associations. *Imagine* was invited to the French national steering committee of the Rare Diseases Networks and contributes to the 2018-2022 French National Plan for Rare Diseases within national workgroups. The Institute is also involved in the 2019 Call for Projects on Rare Diseases (European Joint Program On Rare Diseases) (EJP RD), particularly through its steering committee.

Throughout the year, *Imagine* hosted events organized by the rare diseases networks of the campus and territory, as well as by patient associations. Notably, in 2018, it hosted Pierre Royer genetics seminars, the reference center for rare epilepsy seminars, the General Assembly of the AnDDI-Rares network, seminars of the reference centers for mastocytosis, ophthalmological diseases, constitutional bone diseases, autoimmune diseases, inflammatory rheumatism, genetic deafness, Oscar, G2M, Neurosphynx networks. The Ile-de-France Espace éthique (Greater Paris ethics space) as well as global associative players such as Le Rire Médecin and NOC ("Nous on crée") also organized their events in the conference center.

Opening up

Providing information and sharing with the general public

Providing information and conversation with the general public is essential for the *Imagine* Institute to inform them and help them to understand its activities, advances and projects, and raise awareness on genetic diseases. With this in mind, the Institute opened its doors to the public on several occasions in 2018.

On February 28, 2018, on International Rare Disease Day, the Institute, Hôpital Necker-Enfants malades AP-HP and the rare diseases platform opened their doors. The public had the opportunity to visit the Institute and some of its laboratories, and to take part in fruit DNA extraction workshops. During the AP-HP Open Days on May 24 and 25, 2018, the Institute offered lectures by Prof. Stanislas Lyonnet and researcher Christine Bole-Feysot on genetics, laboratory visits and workshops to students from neighboring schools, the general public and families.

The Institute is also committed to joining the public debates and facilitating the provision of information and public participation in these debates.

2018 was marked by holding the French General States of Bioethics, which aimed to prepare the revision of the bioethics laws. As a pioneering Institute in genetic research, *Imagine* contributed to this preparation. In particular, the Institute hosted the "Genetics, forecasting, decision-making in uncertain situations" lecture in April 2018, and took part in government consultations, as well as in a round table as part of the Senate's work on these laws.

"Imagine *has to stress the challenges of modern genetics, its consequences on the practices of medicine and research, as well as the perception of the company by our fellow citizens. Genetics should not be done in a secret laboratory but in the full knowledge of everyone"*, recalled Prof. Stanislas Lyonnet, Director of the Institute, on this occasion.

The Institute also took part in a draft standard with the objective of contributing to a better understanding of the ethical issues arising from the use of artificial intelligence (AI) in the context of life and earth science, and more specifically in the context of genetics.

EUROPEAN HERITAGE DAYS

On September 15 , on the theme of heritage and "the art of sharing", *Imagine* offered a set of fun activities to gain a better understanding of genetic diseases. Prof. Stanislas Lyonnet presented *Imagine*'s architecture and its unique concept to visitors, who then took part in laboratory and core facilities visits with the researchers. They then discovered genomic sequencing, genetic diseases of the skin, the immunity and the brain. The public was invited to participate in experiments on western blots. The event was a great success, with nearly 1,000 registrations.

SOCIAL REPORTING

UMR 1163 and *Imagine* Foundation

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

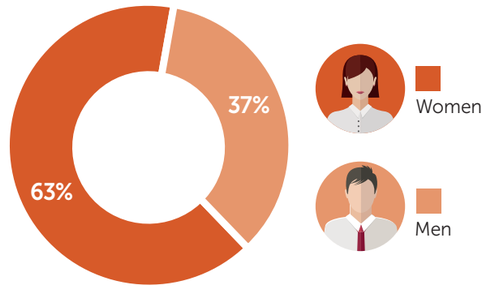
WORKFORCE

Workforce on 12/31/2018

557 PEOPLE

486 FULL-TIME EQUIVALENT (FTE)

Breakdown of employees by gender on 12/31/2018



Staff nationalities on 12/31/2018

AFRICA

ALGERIA: **7** - BENIN: **1** - MOROCCO: **1** - TUNISIA: **1**

AMERICA

ARGENTINA: **2** - BRAZIL: **5** - CANADA: **4** - COSTA RICA: **1**
CHILE: **2** - MEXICO: **2**

ASIA

CHINA: **1** - INDIA: **5** - IRAN: **1** - JAPAN: **3** - LEBANON: **1**
TURKEY: **2** - VIETMAN: **1**

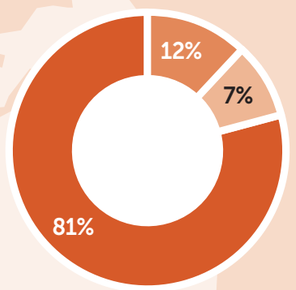
EUROPE

GERMANY: **5** - ENGLAND: **3** - BELGIUM: **2** - BULGARIA: **2**
CROATIA: **2** - DENMARK: **11** - SPAIN: **11** - FRANCE: **448**
FINLAND: **2** - GREECE: **3** - IRELAND: **2** - ITALY: **24** - LITHUANIA: **1** POLAND: **1** PORTUGAL: **5** - ROMANIA: **2** - RUSSIA: **1** - SWITZERLAND: **1**

OCEANIA

AUSTRALIA: **2**

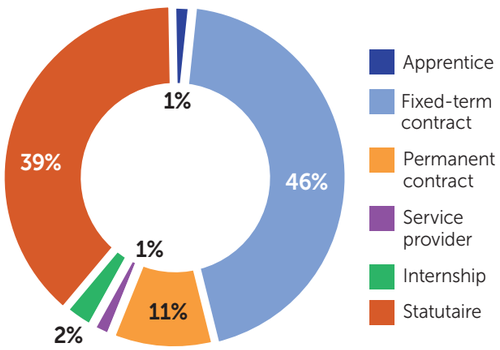
35 NATIONALITIES



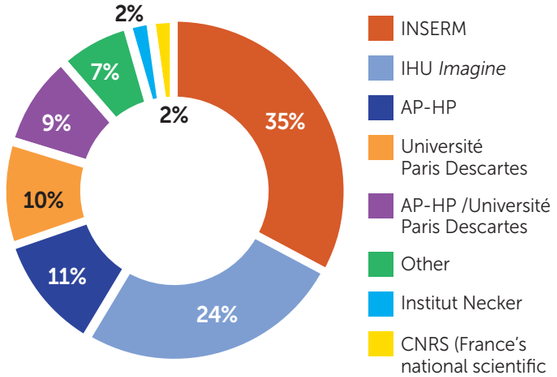
Opening up

JOBS

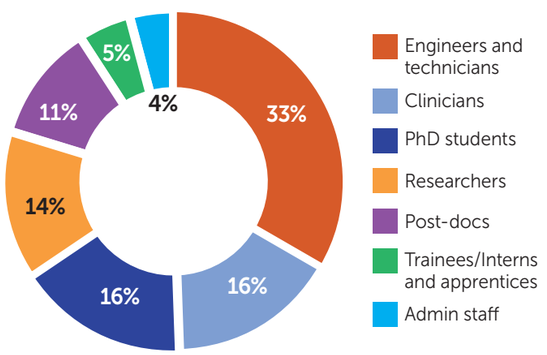
Breakdown of personnel by contract type on 31/12/2018



Breakdown of personnel by employer on 31/12/2018



Breakdown of personnel by job on 31/12/2018



Imagine Foundation

These figures concern only the employees of the *Imagine* Scientific Cooperation Foundation in the strictest sense of the term.

WORKFORCE

157 EMPLOYEES ON 12/31/2018 INCLUDING SECONDMENT

146 FULL-TIME EQUIVALENT (FTE) ON 12/31/2018

146 EMPLOYEES ON AVERAGE IN 2018

138 FTE ON AVERAGE IN 2018

13,5 FTE EXTERNAL PERSONNEL ON 12/31/2018

4 APPRENTICES ON 12/31/2018

New contracts in 2018

9 PERMANENT CONTRACTS INCLUDING **3** FIXED-TERM CONTRACTS TRANSFORMED INTO PERMANENT CONTRACTS

57 FIXED-TERM CONTRACTS

27 FIXED-TERM ASSIGNMENT CONTRACTS

4 APPRENTICESHIP CONTRACTS

14 PAID INTERNSHIPS

Contracts ended in 2018

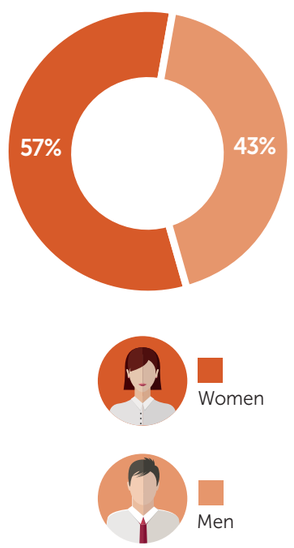
51 FIXED-TERM CONTRACTS AND FIXED-TERM ASSIGNMENT CONTRACTS ENDED

4 FIXED-TERM CONTRACTS EXPECTED TO END

4 PERMANENT CONTRACTS TERMINATED

10 INTERNSHIPS ENDED

Breakdown of personnel by gender on 12/31/2017



Opening up

Nationalities on 12/31/2018

AFRICA

ALGERIA: **2** - TUNISIA: **1**

AMERICA

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

ASIA

INDIA: **1** - IRAN: **1** - JAPAN: **1** - LEBANON: **1**
PHILIPPINES: **1** - TURKEY: **1**

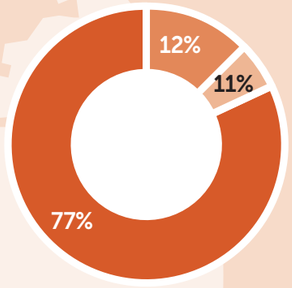
EUROPE

BELGIUM: **1** - CROATIA: **1** - SPAIN: **3** - FRANCE: **113**
ITALY: **10** PORTUGAL: **2** - RUSSIA: **1**

OCEANIA

AUSTRALIA: **1**

21 NATIONALITIES

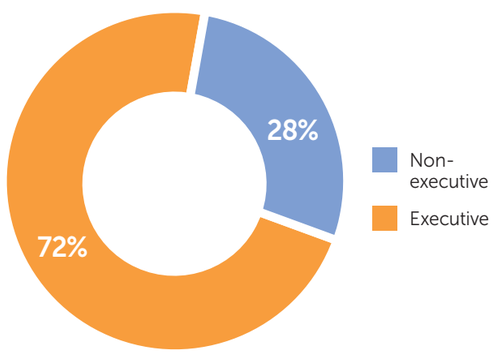


Average age of employees on 12/31/2017

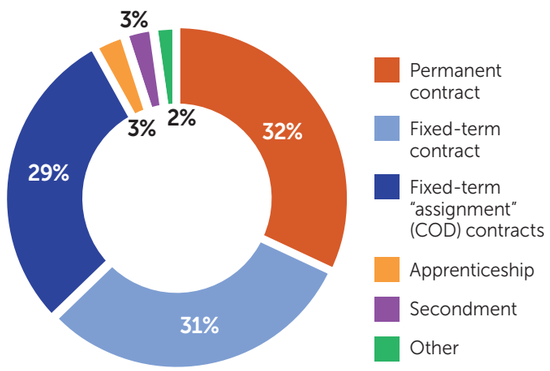
32,3 33,1 32,7

JOBS

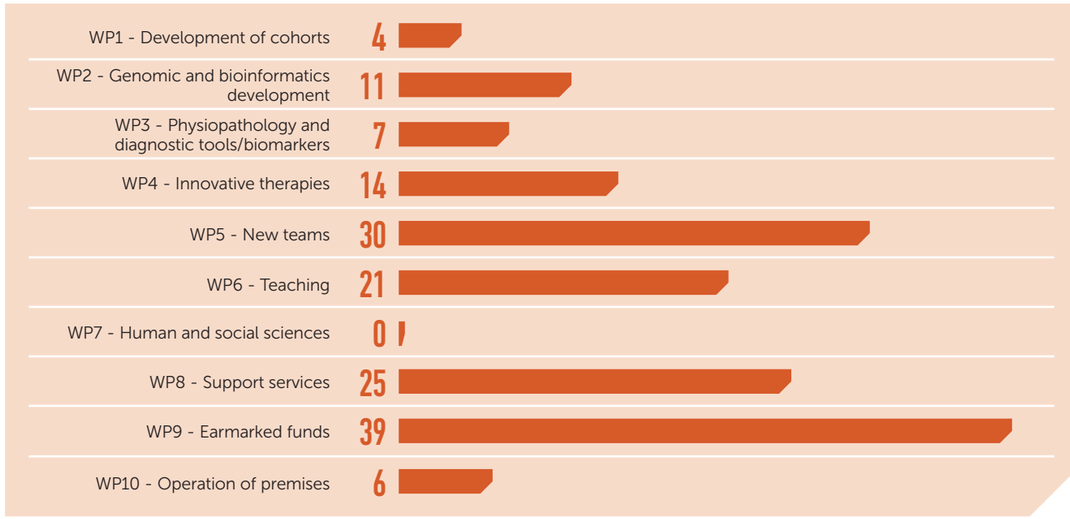
Breakdown of employees by status on 12/31/2018



Breakdown of employees by contract on 12/31/2018



Breakdown of personnel by work package (IHU program) on 12/31/2017



Absenteeism rate in 2018*: 0,61%

*Except for maternity and paternity leave

VOCATIONAL TRAINING

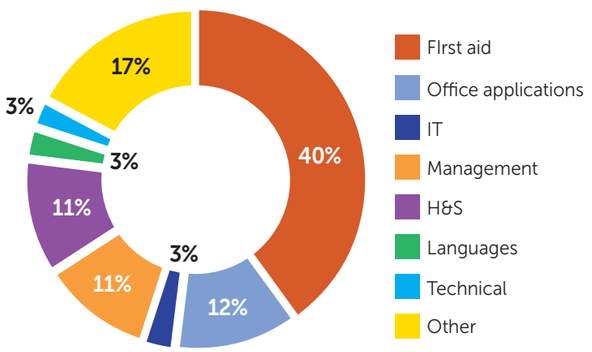
Employees having received training

22 13 35

Number of training hours funded

949,5 907 1856,5

Topics of funded training



INTERNS

Number of interns in 2018:

PAID **16** (1,610 DAYS)
UNPAID **39** (305 DAYS)

Com
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Working alongside doctors and researchers.

> *One of the beautiful things about* Imagine *is not being able to exist without its friends, its benefactors, its sponsors, without the philanthropists who have supported us for years now, with a single weapon, their heart.*

Prof. Stanislas Lyonnet, Director of *Imagine* Institute

Com
mi
ting

"When the strengths come together, so that there is cohesion and unity, it works, and all for the benefit of our children."

Nadia, mom to a young boy with a disease diagnosed after 6 years of diagnostic uncertainty.

magine **is a unique model that combines the best of private and public. Thanks to the support of public authorities, its founders and sponsors, the Institute strives towards its mission to change the lives of families affected by a genetic disease. This combination of funding sources gives the Institute its independence and flexibility to take on the challenge of understanding and curing genetic diseases.**

As a Scientific Cooperation Foundation (SCF), the *Imagine* Institute is authorized to accept gifts, bequests and donations (life insurance capital, for instance). Thanks to the loyal and valuable support of its donors and sponsors, *Imagine* is accelerating discoveries and making every effort to identify the gene involved in young patients with genetic diseases, and to develop the treatments of tomorrow.

Heroes, to accelerate research

On February 12, 2018, the 3rd edition of the "Heroes for *Imagine*" gala was held. The event raised a profit of €7 million thanks to the generosity of 360 "Heroes" and the exceptional contribution of the MSDAVENIR Foundation. Initiated by Kamel Mennour, joined by Didier and Clémence Krzentowski, this auction was hosted by Gad Elmaleh, who presided as master of ceremonies, and by François de Ricqlès and Julien-Vincent Brunie for Christie's. *Imagine* would like to thank the sponsors and partners who, through their invaluable support, contributed to the success of this evening. A special thank you to Dior, LVMH, Marcadé Event, Havas and Interparfums. Thank you to all the collectors, artists and creators, galleries and donors, great houses and well-known figures who are all committed to advancing research on genetic diseases.

Major boost for sequencing

Thanks to the tremendous generosity of its donors during this evening, *Imagine* was able to purchase a NovaSeq, high-throughput DNA sequencer. *"This purchase comes exactly within the scope of the Institute's acceleration strategy, first to name the illnesses: because 1 child in 2 out of the 30,000 who come to Imagine every year have not been diagnosed and this uncertainty is awful for families"*, Prof. Stanislas Lyonnet, Director of *Imagine*, comments *"The NovaSeq will leverage diagnostic capabilities, offer ways to understand diseases and therefore therapeutic options."*

"We had hope when we were told that Imagine was going to get a high-throughput DNA sequencer which would help reduce the diagnosis time. Automatically, the diagnosis time for the child is less time to suffer."

Maureen and Dimitri are the parents of Lila, 5 years old, who suffers from a rare autoinflammatory disease.

Explore the genome's dark matter

During the evening, the MSDAVENIR Foundation also announced a gift of €2.4 million to the Institute for "DEVO-Decode", an ambitious program aiming to explore the role of non-coding DNA in the genome and genetic diseases. For a long time, all eyes have been turned to the coding regions of DNA, those which contain the necessary information in the production of proteins, the linchpins of cells. However, they only make up 2% of the genome. Unknown for a long time, considered in the past as useless, the role of non-coding regions, which therefore represent 98% of our genome, seems to be gaining in importance. This task, compared by some as looking for a needle in a haystack, is tackled by 8 core facilities, 8 research teams, including that of Prof. Yanick Crow, and 8 reference centers at *Imagine*, under the coordination of Stanislas Lyonnet, with the identification of genetic causes of undiagnosed genetic diseases in sight, and new therapeutic approaches in the longer term.

Families committed to advancing research

Imagine also knows that it can count on the support of dozens of families affected by genetic diseases. Through events, their testimony in the press, fundraising organized by them, these families raise money to support the researchers' work at the Institute. For example, this is the case for the parents of Maïa, who is nine and a half years old, and carrier of a KCNB1 gene mutation, diagnosed at the *Imagine* Institute in 2016. It is an extremely rare mutation, recently discovered (end-2014). To date, 70 carriers have been listed worldwide.

However, before becoming a part of this KCNB1 "family", Mélissa and Paul, Maïa's parents, believed for a long time that they were facing this disease alone. Today, Mélissa Cassard is the president of the KCNB1 France association, the only one in the world for this gene up to now, which has already raised €62,000 and therefore helped to launch a dedicated research program at *Imagine*. *"For us, it is a marvelous opportunity"*, Mélissa emphasizes.

As for Noa Lûu, 14 years old, suffering from a genetic disease that prevents her from eating like all other teenagers of her age, she and her family have been supporting *Imagine* for ten years. The whole family regularly take action to sell crêpes and raise awareness in schools. As soon as Noa Lûu has a free moment, she makes bracelets to sell for the benefit of research on her disease, methylmalonic acidemia.

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Promoting and supporting the Institute

To support its fundraising campaigns, in 2018, *Imagine* decided to relaunch its awareness campaign, created in 2017. Thanks to Skill-based sponsorship from the Havas agency, advertising and TV commercials have been published and broadcast across France.

Imagine's image was also given big exposure thanks to the support of Corentin Douguet and Christian Ponthieu. These two sailors competed in the transat, AG2R La Mondiale, in April and May 2018 in *Imagine*'s colors to help accelerate research on genetic diseases.

Loyally supporting the *Imagine* Institute, the Henner Group mobilized its employees for the 3rd consecutive year for the benefit of the Institute. €10,000 has therefore been donated by the group chaired by Charles Robinet-Duffo to help research.

Doctors and researchers themselves are committed. On November 18, 2018, the *Imagine* sport association ran alongside young Raphaël Wacrenier in the Boulogne half-marathon. Thanks to the initiative of Damien Charvillat, his lead instructor, and to the support of the AFG Autisme and Dune D'Espoir associations, this young boy suffering from a rare disease was able to take part in this sports challenge.

Finally, a big thank you goes out to the company, Stella, for donating a custom-made foosball table customized in *Imagine*'s colors: moments to relax offered to sporty members of staff at the Institute.

Promoting education at *Imagine*

Major donor of *Imagine* since 2012, the Fondation Bettencourt Schueller contributes greatly to the Institute's education and training mission. In 2018, the foundation supported the second class of students on the *Imagine* Masters in Bioentrepreneurship, as well as three education and training programs created to support PhD students and encourage young physicians to be trained in research, International PhD and Time for Research programs.

FONDATION BETTENCOURT SCHUELLER

Teddy Riner, unwavering support of children

Imagine sponsor since 2012, Teddy Riner came to meet young patients and medical and scientific teams: his tremendous courage and unfailing optimism are truly infectious! *Imagine* is proud to be able to draw support from this great champion to raise public awareness on the cause of millions of children and adults suffering from complex diseases that are still unknown.

Committed founding members

The *Imagine* Institute is a Scientific Cooperation Foundation: this structure facilitates private and public partnerships. This exceptional combination of private and public funds gives it maximum agility and flexibility, which are key to accelerating research on genetic diseases.

In December, 2018, *Imagine* renewed its multi-year agreements with its six founding members, who therefore renewed their trust in *Imagine* to conduct the IHU scientific project: Inserm, AP-HP, Université Paris Descartes, AFM-Téléthon (the French Muscular Dystrophy Society), the City of Paris and the Fondation Hôpitaux de Paris-Hôpitaux de France (Paris Hospitals Foundation - an association focused on improving the quality of life of hospitalized children, teenagers and elderly persons).

In 2018, the operating and investment budget provided by the *Imagine* Institute's founding members (Inserm, Université Paris Descartes, AP-HP) was €40 million.

To this operating budget, *Imagine* combines an "acceleration" budget of €19 million as part of its French University Hospital Institute (IHU) accreditation. The latter allows it to provide its research teams with the best talents and equipment in order to multiply discoveries on behalf of patients.

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Thank you to everyone!

To all of our donors, to our founding members, our institutional and private partners, to the patrons who have been open to our ventures from the start, committed with us for many years, to our unwavering support.

Here is the list of our sponsors, in alphabetical order:

Fondation Bettencourt Schueller

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DGM - Shahan Sheikholeslami, Hugues Schmitt

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Fondation EDF

Galerie kreo – Didier and Clémence Krzentowski

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Stella

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Viva Model Management

FINANCIALS

This marks *Imagine*'s eleventh fiscal year. Fiscal Year 2018 is a new stage in the development and consolidation of *Imagine* Institute. This fifth year of operations since opening our new building is the second year of operations of the 2016-2025 roadmap signed in December 2016 by the founding members. During Fiscal Year 2018, the *Imagine* Institute welcomed a new team (E. Kabashi), continued its training programs through and for research, launched its funding programs of cross-functional and value-creation research projects (Cross-lab and Innogrant), confirmed its technological innovation dynamics focused on pathophysiological platforms through a substantial amount of investment, and was able to convince it donors of the relevance of its research strategy through significant fundraising, particularly during the third edition of the Heroes charity gala.

Fiscal Year 2018 reflects the extremely positive growth dynamics of funds made available by the Institute, following Fiscal Years 2016 and 2017, through public or private subsidies and industrial agreements signed by the Institute. Such momentum results in a surplus, thanks to commitments regarding increased and collective funds and having committed to the 2018 projected investment plan.

The overall analysis of the 2018 financial statements provided the following figures.

BALANCE SHEET

The balance sheet is a financial statement summarizing *Imagine*'s assets and employment of resources on the reporting date, December 31, 2018.

On this date, it shows a balance of **€35,866,105** vs **€30,620,626** in 2017 (+17%).

On December 31, 2018, the breakdown of *Imagine*'s assets was:

Net assets	Net liabilities
1. Capital assets: €9,036,934 (+3%) (notably representing the value of *Imagine*'s platforms and equipment)	**3. Charitable funding: €17,695,296 (+4%)** (initial and additional endowment, profit/(loss) for the fiscal year and investment subsidies)
2. Circulating assets: €26,829,172 (+23%) (representing investments and accounts receivable)	**4. Provisions for liabilities and charges: €936,609 (+9%)** (VAT and retirement allowance provision)
	5. Earmarked funds: €8,975,106 (+18%) (operating subsidies)
	6. Debts: €8,259,094 (+62%) (bank loans, accounts payable, tax and social security liabilities and deferred income)

Intangible assets and property, plant and equipment

Thanks to the success of the Heroes charity gala in February 2018 and the advances of the gene therapy Domaine d'Intérêt Majeur (DIM) research program in the Ile de France (Greater Paris) region coordinated by *Imagine*, the Institute was able to get new equipment essential to maintaining its level of technological capability such as a very high-throughput sequencer allowing the whole genome and exome to be explored at a highly efficient cost and time frame. It also acquired a storage server for bioinformatics processing of sequenced data, respectively by the genomics and bioinformatics facilities, and an imager for the animal facility.

The amount of fixed assets at end-2018 is €20.8 million (vs €19.0 million in 2017), including €14.5 million in laboratory equipment.

Long-term investments

In 2018, the company Step Pharma, in which *Imagine* holds shares, completed a new round of fundraising of more than €2.2 million and presented encouraging prospects on its development. Given these items, the value of the securities held could be confirmed in long-term investments.

Receivables

Receivables have increased on December 31, 2017 following the increase of funds and relative invoicing, and the postponed settlement of the client Alexion, hosted by *Imagine* until November, 2018 and for which the departure conditions are being negotiated.

Earmarked funds

In accordance with the chart of accounts for voluntary organizations and foundations, earmarked funds are on the liabilities line that shows, at the year-end, the share of resources allocated by third party funders for specified projects, and which were not used in accordance with what they were set aside for. They came to €8,975,106 as at end-2018 and were made up of €4.8 million in provisions on the non-expendable endowment, ANR-IHU, €1.8 million on other public subsidies and €2.3 million of the amount of donations.

Debts

Debts include deferred income in industrial contracts for €2,116,091, up 50% on 2017 due to the development of these contracts. Accounts payable increased significantly at end-2018. On the one hand, they increased because of subsidies to the Greater Paris region - DIM gene therapy and ANR-RHU C'IL LICO, received at the end of the fiscal year and to donate partly to member partners. On the other hand, they increased because of the offset in early 2019 of the very high-throughput sequencer payment to the company, Illumina.

INCOME STATEMENT

The 2018 income statement takes account of all the positive and negative cash flows or other transactions that modified *Imagine*'s financial position in 2018; income generates assets and expenditure reduces them in the course of the Institute's activity.

Imagine Institute's income statement was as follows:

- Income: €22,984,543 (vs €18,349,515 in 2017, €16,80,238 in 2016 and €19,155,981 in 2015),
- Expenditure: €2,014,200 (vs €1,959,450 in 2017, €14,841,491 in 2016 and €14,373,478 in 2015).

The surplus amounted to €970,343 in 2018, versus a profit of €1,390,127 in 2017.

2018 income

Imagine's income increased again in 2018: up from €10 million in 2014 to €19.1 million in 2015 (including €1.2 million from regularization of the recovery of VAT on purchases from previous fiscal years and €2.4 million from reversals of earmarked funds) then fell back to €16.8 million in 2016. It reached €18.3 million in 2017 and €22.9 million in 2018 thanks to the development of industrial contracts and core facilities, the increase of public and private subsidies received and the results of the 2018 Heroes event.

This figure includes operating income, investment income and exceptional items.

Operating income rose from €9 million in 2014 to €14.8 million in 2015. It ended at €14.4 million in 2016, €15 million in 2017 and reached €18.9 million in 2018.

Service provisions continued to grow rising from €1.2 million in 2015 then €1.9 million in 2016, €2.46 million in 2017, reaching €2.89 million in 2018 due to the dynamic of industrial partnerships (€1.069 million in 2016, €1.652 million in 2017, €1.856 million in 2018 to which €2.05 million of deferred income to be deducted in 2019 is added) and the strong growth of platform services (€313,000 in 2017, €700,000 in 2018, including €404,000 for the genomics core facility).

Gifts also strongly increased in relation to previous fiscal years, which explains the growth seen in "Other income", rising from €3.35 million in 2017 to €6 million in 2018. In 2016, this item amounted to €4.54 million.

Financial income slightly decreased in 2018, as money markets remained flat (€72,928 in 2018 vs €91,004 in 2017, €44,514 in 2016, €50,672 in 2015 and €71,451 in 2014).

Exceptional income (€525,064) corresponds to the share of investment subsidies recognized in income of which the natural decrease is partially offset in 2018 by the registration of a new investment subsidy in the context of the 2018 section of DIM gene therapy. Added to that is exceptional income of €31,000 related to the sale of shared equipment. In 2018, exceptional income amounted to €525,000 vs €580,000 in 2017.

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2018 expenditure

Imagine's 2018 expenditure rose by 29% reaching €22 million versus €17 million in 2017, €14.8 million in 2016 and €14.4 million in 2015. This figure includes operating expenditure, interest expenses and exceptional items.

Operating expenditure stood at €17 million in 2018 versus €13.8 million in 2017, €12.9 million in 2016 and €10.4 million in 2015.

Expenditure was marked by a rise in the operating expenses of the Institute, directly linked with the development of hosting contracts in industrial partnerships or public subsidies and efforts within the IHU program as expected in the roadmap, with the installation and ramp-up of the new teams, strengthened technology platforms and technology transfer initiatives.

Between 2017 and 2018, operating expenditure increased by €3.234 million, owing to an increase in consumables (+€502,000) and services (+€364,000) by research teams but also a rise in payroll of nearly €1 million between 2017 and 2018. Transfers of €387,000 to DIM and RHU partners also appear in the operating expenditure and drive growth of "subsidies provided by the association".

Exceptional interest and exceptional expenses vary between 2017 and 2018 due to the exit of equipment that has not yet completely depreciated when it is no longer part of *Imagine*'s assets.

Caroline YOUNG, Treasurer

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