ACTIVITY REPORT 2020

IMAGINE, CURING GENETIC DISEASES

imagine

INSTITUTE FOR GENETIC DISEASES

IMAGINE

HISTORY

2007

The Fondation *Imagine* was created by its founding president, Claude Griscelli. Six founding members AP-HP (Paris public hospitals authority), Inserm, Université Paris Descartes (now the Université de Paris), Paris City Council, AFM-Téléthon and the Fondation des Hôpitaux.

2008

1st recruitments,

1st platforms and 1st equipment.

2009

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

2011

Granted Institut Hospitalo-Universitaire (IHU – University hospital institute) status as part of the Investissements d'Avenir (PIA) (Investments for the Future) Program.

2012

1st recruitment of international teams.

Teddy Riner becomes *Imagine*'s sponsor.

2014

Inauguration of the *Imagine* building.

2015

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

2016

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

2017

Launch of the RHU C'IL-LICO project: "Médecine du futur pour les ciliopathies avec atteinte rénale" ["Medicine of the Future for Ciliopathies with Renal Involvement."]

Granted the Major Field of Interest (DIM) status for gene therapy, funded by the Ile-de-France (Greater Paris) region.

2018

Assessment of the Institute's 24 research laboratories by Haut Conseil de l'Evaluation de la Recherche et de l'Enseignement Supérieur (HCERES – High Council for Evaluation of Research and Higher Education).

A total of 25 rare disease reference centers on the Hôpital Necker-Enfants Malades AP-HP (Necker children's hospital, part of the Paris hospital authority) campus affiliated to *Imagine*, as well as four associate laboratories.

2019

Launch of the RHU ATRACTion project: "Déficits immunitaires primaires avec auto-immunité ou auto-inflammation" ["Primary immunodeficiency with autoimmunity or autoinflammation"].

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

2020

Institut Carnot accreditation.

6 new reference centers for rare diseases are affiliated with *Imagine*, taking the number up to 31.

TABLE OF CONTENTS

imagine
INSTITUTE FOR GENETIC DISEASES

EDITORIAL

CROSS INTERVIEWS

2020 was marked by an exceptional crisis. What was the impact for the Institute?

Stanislas Lyonnet, director of Institut *Imagine:* As we write this report, we are still in the third wave of the Covid-19 pandemic. Our thoughts go first and foremost to our medical and nursing colleagues at the Necker-Enfants Malades AP-HP campus and throughout France and the world, who have been working for over a year and a half now to take in patients and provide them with the best care under extremely stressful circumstances. I would like to thank them for their commitment during this unprecedented crisis. Let us also pay tribute here to the extraordinary mobilization of all scientists and doctors, which allowed us to progress at a crazy speed to understand Covid-19, its treatments, and to create vaccines less than a year after its start, a real achievement.

This exemplary spirit was fully alive at *Imagine*. Our teams, whether involved in genetic disease research, Covid-19 research and care, or supporting doctors and researchers, have been driven by solidarity and commitment. Thanks to them, we have been able to pursue our research and care work for patients and their families, often at full capacity, while fully complying with health security measures.

Laure Boquet, General Delegate of Institut *Imagine:* *Imagine*, under very poor conditions, has managed to stay fully committed to its scientific work, with unparalleled agility, inside or outside its own premises, thanks to the collective commitment of all the staff. This crisis has shown once again, and in very powerful way, that *Imagine* is first and foremost about men and women committed to a cause. We are very proud of them; they are an inspiration, and a sign of solidity for the future. I would like to thank the teams of the Institute, but also those on our university hospital campus, our founding members for their support during this crisis, as well as our friends and loyal supporters, once again by our side, for their unfailing presence, even if our fundraising events had to be postponed.

Arnold Munnich,president of the Fondation *Imagine:* What guides *Imagine* is the children. The fight against genetic diseases has not stopped because of the crisis. We have remained focused on our fight. These children and their families are hit even harder by the crisis, and we must continue to move forward ever faster, whatever the cost, for them.

Has the Institute continued to speed up research and care despite everything?

Arnold Munnich: The research teams have been highly mobilized, and they made many discoveries, making it possible to better understand, diagnose and sometimes treat genetic diseases. The clinical research teams, highly impacted by the crisis, were at hand to ensure the continuity of clinical trials and patient care. Major structural transversal projects have been launched at the Institute and throughout the country, giving new hope for diagnosis and treatment.

Laure Boquet: With our main concern driving us on and our ambition to change the lives of families affected by genetic diseases, we have endeavored to open the Institute to families and patient associations. We have launched human and social science programs and projects to support the life course of patients and their relatives, from seeking a diagnosis to care and follow-up, as well as reflecting on the consequences of the disease, while considering the sociological, psychological, linguistic and artistic implications. We want to unite these energies to look beyond the lab bench and patient care.

Stanislas Lyonnet: Even before the March 2020 lockdown, several Institute teams had already entered the race against Covid-19. Using their knowledge of genetic diseases, they helped to improve understanding of the virus and the disease, some aspects of which are similar to abnormal immune reactions that they have already studied in other circumstances. Major discoveries have been made by these teams and have constituted a huge advance in research, screening and patient care. This is another example of the impact of research on genetic diseases, even rare ones, on much more common diseases, and of the agility of a hospital-university institute (IHU), capable of leaping into action in an emergency, and making findings for many, while only seeking for a few.

What are the two key words for the future?

Laure Boquet: Adaptation and openness.

Arnold Munnich: Genetic diseases and families.

Stanislas Lyonnet: Innovation and humanism.

Today, one in two children still has still not been diagnosed. We will do everything possible, through an ambitious roadmap, and with a child-centered approach, to accelerate and fill the diagnostic gap as quickly as possible, and to achieve a rate of 80% of children diagnosed and double the therapeutic solutions available.

A word from Claude Griscelli, founding president of *Imagine:*

At Imagine *the motivations of each person, whatever his or her functions, are behind the deep desire to put sick children at the center of everything, at the center of the virtuous loop that starts from a desire to understand the genesis of their ailments, and return them to treat them more effectively, or at least give them as well as others to come, some relief. We are proud that this state of mind has continued since the creation of the Institute and has not been tainted by the crisis; on the contrary, it has been the driving force behind our mobilization.*

KEY FIGURES

2020

1 000
RESEARCH AND HEALTH PERSONNEL UNITED AROUND THE SAME CAUSE

24
IN SITU BASIC AND TRANSLATIONAL RESEARCH LABORATORIES

17
TECHNOLOGICAL PLATFORMS

4
ASSOCIATED LABORATORIES AT THE HÔPITAL NECKER-ENFANTS MALADES

773
SCIENTIFIC PUBLICATIONS (WITHIN THE IHU SCOPE)

38
NATIONALITIES

32%
OF DOCTORAL AND POST-DOCTORAL STUDENTS AND GRADUATES/ UNDERGRADUATES

OVER
30 000
IN SITU CONSULTATIONS

6
INTEGRATED RESEARCH AND CARE PROGRAMS (ICARPS)

31
AFFILIATED RARE DISEASE REFERENCE CENTERS

7
AFFILIATED HOSPITAL UNITS (8 IN 2021)

2
CLINICAL INVESTIGATION CENTERS

MORE THAN
500
ONGOING CLINICAL STUDIES WITHIN THE IHU SCOPE

OVER
140 000
SAMPLES (BIOLOGICAL RESOURCE CENTER)

57
PATENT FAMILIES AND PIECES OF ACTIVE SOFTWARE

MORE THAN
5 M€
OF INDUSTRIAL PARTNERSHIP CONTRACTS WON IN 2020

NEARLY
3.7 M€
COLLECTED (DONATIONS, PRIVATE GRANTS AND PATRONAGE)

6
ERC (EUROPEAN RESEARCH COUNCIL GRANTS) ONGOING, INCLUDING 2 CONSOLIDATED ERC

THE 6 FOUNDING MEMBERS OF *IMAGINE*:

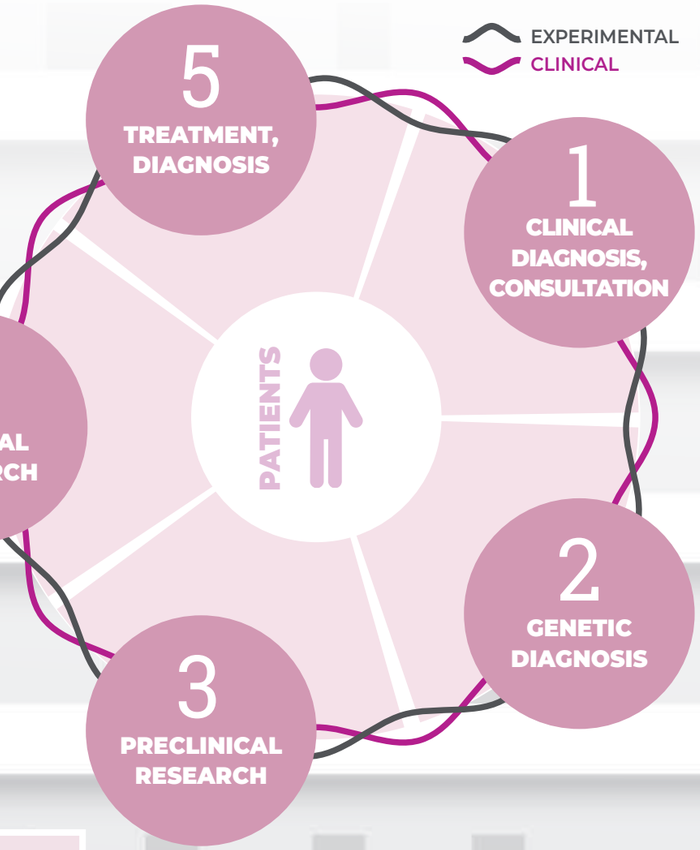
ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS · Inserm La science pour la santé From science to health · Université de Paris · fondation des hopitaux · MAIRIE DE PARIS · AFM TÉLÉTHON INNOVER POUR GUERIR

Imagine's scientific and clinical scope

24 RESEARCH TEAMS

17 TECHNOLOGICAL PLATFORMS

1000 RESEARCH AND CARE STAFF



4 ASSOCIATED LABORATORIES

31 REFERENCE CENTERS FOR RARE DISEASES

PLAN NATIONAL MALADIES RARES 2018-2022

7 AFFILIATED CLINICAL SERVICES

2 CLINICAL INVESTIGATION CENTERS

THE 6 FOUNDING MEMBERS OF *IMAGINE*:

HIGHLIGHTS

Imagine granted Institut Carnot label

The step was taken in 2020 for *Imagine* from "Tremplin" to "Institut" Carnot. Transforming researchers' scientific advances into diagnostic and therapeutic innovations is one of the Institute's missions. Obtaining "Institut Carnot" label marks the recognition of the quality and dynamism of *Imagine*'s industrial relations by the Ministry of Higher Education, Research and Innovation, and represents an important step for the development of the Institute and care for patients with genetic diseases.

"Carnot Institute labelling is awarded for four years. It will enable us to significantly grow and fund our R&D partnership development efforts. This label also provides our partners with a guarantee that collaborative projects are examined and implemented in line with best practice," explains Romain Marlange, director of the Innovation and Technology Transfer Department at Institut *Imagine*. *"The promotion of our research and the involvement of industrial partners are essential for bringing life-changing innovations to patients with rare genetic diseases as quickly as possible".*

Imagine thanked its founding members for their support, and congratulated AP-HP, which was also given Institut Carnot labelling.

Imagine inaugurates its LabTech Single-Cell@*Imagine*

On 14 October 2020, *Imagine* inaugurated, in the presence of Pierre-Antoine Molina, Prefect, General Secretary for Public Policies of the Prefecture of the Ile-de-France Region, and the President of the Ile-de-France Region, Valérie Pécresse, a technology hub unique in Europe, the LabTech Single-Cell@*Imagine*. Directed by Mickaël Ménager, it brings together the human and technological skills as well as the equipment needed to analyze the expression of thousands of genes cell by cell, and to dive into the heart of cells with a level of precision never attained before, to take a fresh look at genetic diseases.

The technology, developed by 10X Genomics, offers the possibility of establishing a real cellular identity card for each individual. This information will supplement other patient data and can be compared with that of different known pathologies, in order to make a diagnosis. *"This unique technology development laboratory is boosting the skills of the* Imagine *Institute in research on genetic diseases. This is a major step towards truly personalized medicine,"* explains Prof Stanislas Lyonnet, director of *Imagine*.

This laboratory received €0.6 million in support as part of the SESAME call for projects for PIA programs in 2019. It is accessible to all *Imagine* laboratories and, more broadly, to all researchers in the Ile-de-France region, whether academic or industrial.

The French President visits Institut *Imagine*

On 4 December 2020, the French President, Emmanuel Macron, visited Institut *Imagine* accompanied by the Minister of Solidarity and Health, Olivier Véran, and the Minister of Higher Education, Research and Innovation, Frédérique Vidal. After a long visit of the Institute, meeting many patients, families, doctors and researchers, the French President asked to talk to the teams of Laurent Abel and Jean-Laurent Casanova, directors of the Laboratories of Human Genetics of Infectious Diseases at *Imagine*, pioneers in learning about the role of genetics in the development of serious forms of Covid-19. The President finally shared his vision on health research and innovation for the coming years during a meeting with the sponsors of the campus project dedicated to digital health, the Val de Grâce project.

The French President described *Imagine* as a *"model to be consolidated and brimming with lessons to be learned"*, and stressed its *"pioneering ability to attain flexibility and speed, break barriers, and decompartmentalize for the benefit of healthcare"*. He chose a unique and catalytic place of innovation to present his ambition to build ecosystems at the intersection of research, innovation and industry.

AWARDS AND REWARDS

- **Prof. Jean-Laurent Casanova**

  Appointed Chevalier de la Légion d'Honneur

  Appointed member of the Covid-19 Scientific Council, tasked by the government to inform the public decision on the management of the health crisis.

- **Prof. Françoise Denoyelle**

  Appointed Chevalier de la Légion d'Honneur.

- **Dr Anne Durandy-Torre**

  Appointed Officier de la Légion d'Honneur.

- **Prof. Alain Fischer**

  Appointed to head the National Steering Committee on Covid-19 Vaccine Strategy.

- **Prof. Stanislas Lyonnet**

  Appointed Officier de la Légion d'Honneur.

- **Dr Matias Simons**

  Carl Ludwig Award from the German Society for Nephrology.

ADAPT, ENGAGE, ACCELERATE

"The fight against genetic diseases that is the driving force behind Imagine *continued regardless in 2020. While the Institute had to temporarily bend and adapt its activities to the health situation, its spirit was not tainted. On the contrary, it is with incredible solidarity that* Imagine *mobilized its forces to continue to speed up research, remaining more focused than ever on families affected by genetic diseases, while engaging with agility and determination in the scientific response to the viral pandemic".*

Prof Stanislas Lyonnet,
director of Institut *Imagine*

As Imagine *sponsor Teddy Riner told researchers in April 2020, "I know that, even remotely, you are continuing to advance knowledge of genetic diseases and help children suffering from them. Because the struggle has not stopped there either. The disease continues to affect families, and it is through your daily work that they regain hope. Despite this crisis, which is keeping many of you away from your laboratories, I know that you have all the skills required to innovate, bounce back and continue to move forward. With you, research against genetic diseases is gaining pace, whatever the obstacles, for the benefit of sick children".*

Teddy was right. Doing research requires a lot of creativity, and this year researchers need it to continue their work despite the pandemic, taking into account health constraints, and to continue to generate knowledge for children with genetic diseases.

The spirit of *Imagine* lived on

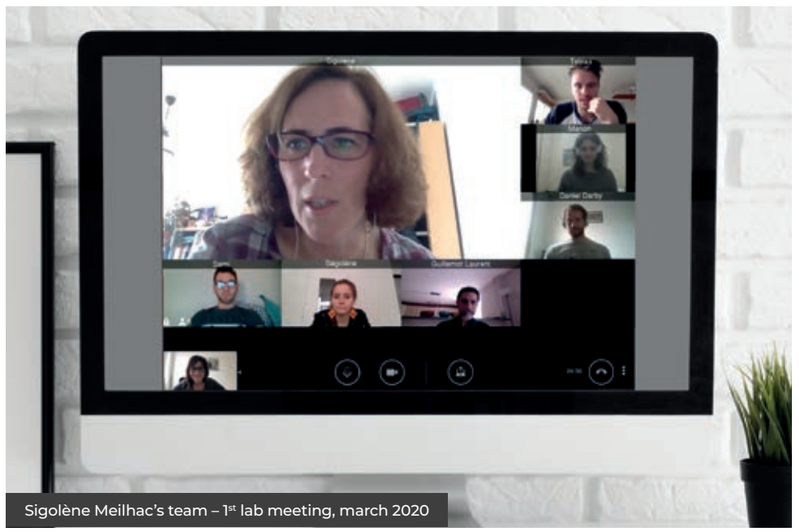
Imagine was forced to reduce the number of people in the on-site teams for much of the year and give priority to remote working. That's fine. In hospital departments, research laboratories, or behind their computers, doctors, researchers, engineers, students, without giving an inch, remained focused on one objective: exploring genetic diseases to better understand them. And this unique knowledge of most-often rare diseases has also proved very useful for deciphering the mechanisms of SARS-CoV2 infection.

Although the keyword was "adapting", the researchers also took advantage of this period to enrich the scientific life of their laboratory. *"We were able to take advantage of this time working from home to deepen bioinformatic and bibliographic analyses, write articles and reports and reflect on the team's future projects,"* explained Sigolène Meilhac, director of the Heart Morphogenesis laboratory, in April. In November, her team published, in *Developmental Cell,* the results of 3D observation of the transformation of the tube serving as a blueprint for the future heart in the mouse embryo, specifically following Nodal gene, which plays a part in asymmetry. *"Nodal has long been known to define the left side of the body," says* Sigolène Meilhac. *"We observed that its action was transient and takes place early on in heart cells, before the heart starts beating."*

And as Mickaël Ménager, director of the laboratory for inflammatory responses and transcriptomic networks in diseases, pointed out: *"Even though, as scientific team leaders, we are accustomed to having to be mobile and teleworking, the period was nonetheless new for everyone. What mattered was being able to stay in touch and maintain a lively laboratory life. Social media and chat tools have been invaluable in communicating easily and quickly."* Moreover, the young researcher remained focused on the future throughout this period, since on 14 October he inaugurated a brand-new laboratory, the Labtech Single-Cell@*Imagine*, equipped with the latest technologies for the analysis of single cells (learn more on page 38)

Conferences that even though virtual, remained very valuable

Quickly, scientific seminars and conferences, places for exchange and knowledge sharing, became virtual, which enabled interactions between physicians and researchers, so important for advancing knowledge. As of Monday, March 30, 2020, less than 15 days after the start of the first lock-down, a virtual seminar brought together more than 410 *Imagine* researchers for the emergency scientific programs launched at the Institute in response to Covid-19. There is also the largest European genetics conference, ESHG 2020, which took place in June with no fewer than 8 speeches by *Imagine* researchers. In early September, Jean-Michel Rozet, director of the Laboratory of Ophthalmological Genetics, organized a seminar bringing together scientists and clinicians to lay the foundations for future cooperation projects on genetic eye diseases. From 14 to 17 October, a dozen researchers from the Institute were present virtually at the conference of the European Society of Immunodeficiencies (ESID), an important meeting in the field of immunology, whose objective is to promote recent research as well as cooperation between all those involved in the diagnosis and treatment of these diseases. The Institute has also maintained a plethora of scientific exchanges thanks to virtual scientific seminars every Monday, presented by members of the Institute or their guests.



Sigolène Meilhac's team – 1st lab meeting, march 2020

"Despite an unbelievable year, Imagine continued to explore genetic diseases, based on 3 essential pillars: naming the disease, identifying the gene or genes responsible, understanding it, studying the disorders caused by the mutated gene or genes, and finding treatments," recalls Prof. Stanislas Lyonnet, director of the Institut *Imagine*

NAMING THE DISEASE

- Discovery of a mutation in the *NOS2* gene explaining **why a seemingly benign cytomegalovirus infection can become fatal** | Jean- Laurent Casanova and Laurent Abel teams | *New England Journal of Medicine*
- Discovery of mutations in the *SMO* gene, a gene known in carcinogenesis, in a large number of developmental abnormalities affecting the brain, heart, skeleton and digestive tract, with variable combinations making it possible to **recognize syndromes classified in the ciliopathies group** | Jeanne Amiel Team | *American Journal of Human Genetics*
- Highlighting the heterogeneous nature of the production of cell lines from human hematopoietic stem cells and progenitors in gene therapy, and **new methods of hematopoietic analysis and differentiation** | Isabelle André Team | *Blood*
- Discovery of mutations in the *RIMS2* gene that causes a **new rare eye disease**, with consequences for the treatment of visually impaired children | Jean-Michel Rozet Team | *American Journal of Human Genetics*
- Discovery of a **new form of syndrome of Mendelian predisposition to mycobacterial infections** linked to an interferon gamma mutation. 1st discovery in this gene coding for cytokine, key to antimycobacterial immunity | Jean-Laurent Casanova and Laurent Abel Teams | *Journal of Clinical Investigation*
- Development of a **statistical method for the identification of genetic signatures** and the recognition of cellular identity at individual cell level | Antonio Rausell Team | *Nature Biotechnology*
- 1st description of a *SOCS1* gene deficiency with possible implications for the **development of quite a wide range of autoimmune diseases** ranging from cytopenia to lupus and psoriasis | Frédéric Rieux-Laucat Team | *Nature Communications*
- Study of the role of the Nodal gene in **implementing the asymmetric architecture of the heart**, essential for it to function properly | Sigolène Meilhac Team | *Developmental Cell*
- Discovery of two new genes, *LSM11* and *RNU7-1*, involved in **Aicardi-Goutières syndrome** | Yanick Crow Team | *Nature Genetics*
- Uncovering the role of mutations in the *MINPP1* gene in the occurrence of pontocerebellar hypoplasia, **serious neurodegenerative diseases in young children** | Vincent Cantagrel Team | *Nature Communications*
- Discovery of a new genetic origin with Mendelian predispositions to mycobacterial infections, by mutation of the transcription factor *T-bet*, which provides **better understanding of the mechanisms of the immune response** | Jean-Laurent Casanova and Laurent Abel Teams | *Cell*

UNDERSTANDING THE DISEASE

- Discovery of a **new programmed cell death process** leading to the elimination of a subtype of transient immature neurons required for the cabling of cortical circuits to function properly | Alessandra Pierani Team | *E-life*
- Discovery of a **deficiency in DNA repair proteins,** PAXX and XLF, in the development and maturation of the hemo-lymphoid system | Jean-Pierre de Villartay and Patrick Revy Team | *Journal of Biological Chemistry*
- Development of an approach combining experiments and computational biology **to map the innate response following HIV-1 infection** in dendritic cells, thereby enabling a better understanding of the dysregulated immune response in many genetic diseases | Mickaël Ménager Team | *Cell Report*
- Highlighting the role of the *FGFR3* gene in **osteogenesis and "welding" of skull bones** in zebrafish | Laurence Legai-Mallet Team | *Journal of Bone and Mineral Research*
- Development of a **model for the study of amyotrophic lateral sclerosis:** a zebrafish line with an *FUS* gene mutation | Edor Kabashi Team | *Neurobiology of Disease*
- Demonstration of the benefits of **identifying places of interaction between T lymphocytes and innate lymphoid cells** to better understand them | Nadine Cerf-Bensussan Team | *Mucosal Immunology*
- Highlighting the role of the COPA gene, which causes a **rare autoinflammatory disease**, in inducing type-1 interferons, one of our body's first lines of defense against viral infections | Yanick Crow Team | *Journal of Experimental Medicine*
- Identification of the X chromosome region responsible for **nephrotic syndrome** with cataracts, hearing impairment and enterocolitis | Sophie Saunier Team | *Proceedings of the National Academy of Sciences*
- Review of the pathological effects of PRPS1 gene alteration, from **isolated hearing loss to severe congenital encephalopathy** | Jeanne Amiel Team | *European Journal of Medical Genetics*
- Identification of the major role of immune response by type-1 interferons against the **Herpes simplex virus** | Jean-Laurent Casanova and Laurent Abel Teams | *Journal of Clinical Investigation*
- Genetic and phenotypic analysis of an extremely rare genetic disease, **leukoencephalopathy**, with calcifications and cysts | Yanick Crow Team | *American Journal of Medical Genetics*
- Description of the various innate immune errors involved in the **immune response to Candida Albicans** and their impact in patients with other conditions | Jean-Laurent Casanova and Laurent Abel Teams | *American Journal of Human Genetics*

FINDING TREATMENTS

- Discovery of the *CTPS1* gene as a therapeutic target of **interest for inhibiting the proliferation of pathological T cells**, including lymphomas | Sylvain Latour Team | *Journal of Clinical Investigation*
- Highlighting the efficacy of Ruxolitinib in panniculitic **T-cell subcutaneous lymphoma** and hemophagocytic lymphohistiocytosis | Gaël Ménasché and Fernando Sepulveda Team | *Blood Advances*
- Discovery of a mutation in the *RAC2* gene associated with bone marrow hypoplasia and **severe combined immunodeficiency** | Isabelle André Team | *Haematologica*
- Analysis of **HPV lesions** that can lead to new diagnostic, preventive and curative approaches in patients | Jean-Laurent Casanova and Laurent Abel Teams | *Human Genetics*
- Discovery of a genetic cause for **early-onset inflammatory bowel diseases** opening up a possible therapeutic pathway | Nadine Cerf-Bensussan Team | *Gastroenterology*
- Discovery of a quick way to identify and characterize blood cells infected with the **Epstein-Barr virus** | Sylvain Latour Team | *Journal of Experimental Medicine*
- Highlighting the role of the molecular motor, kinessin 1, in the "preparation" of **dendritic cells, immune sentinels,** and then in the in vivo anti-tumor response | Gaël Ménasché and Fernando Sepulveda Team | *Nature Communications*
- Discovery of a mechanism for repairing double-stranded breaks in DNA that can become a **basis for cancer therapy** | Patrick Revy and Jean-Pierre de Villartay Team | *Nature Communications*

Clinical research

By bringing together researchers, doctors and patients who come for consultations in the same building of the Hôpital Necker-Enfants Malades AP-HP, Institut *Imagine* creates the right conditions to go even further and faster, taking a “loop” approach: clinical observation, analysis and understanding of the causes and mechanisms of diseases foster the discovery of new diagnoses and treatments. In this loop, clinical research is an essential link in the deployment of scientific innovations and the development of new diagnostic and therapeutic approaches that improve patient care. *Imagine* has made it one of its priorities.

Promoting clinical trials

Once laboratories have gathered all the necessary preclinical evidence on potential treatments or diagnostic methods, the next step is clinical development, which means in patients. To this end, Institut *Imagine* is deploying a system to help set up and conduct clinical trials to assist medical and research teams. This system for accelerating clinical research is divided into 4 complementary areas: support for the investigation (i.e. conducting clinical trials) by supplying the Reference Centers for Rare Diseases (CRMR) with specific clinical research skills; seed funding to launch projects awaiting external funding; regulatory, methodological and ethical support, particularly for processing biological sample collections and personal health data; and finally assistance in setting up clinical research projects with institutional support – mainly AP-HP or Inserm.

“The transition from fundamental research to clinical trials is a long process; we help the researchers and clinicians of our founding members, namely AP-HP, Inserm and the Université de Paris throughout this process, which requires specific expertise. First of all, the feasibility of the study must be assessed, assistance must be provided for setting up the project and drafting the protocol, regulatory submissions made, patients have to be selected, and the issues that arise on a day-to-day basis need to be managed,” explains Salma Kotti, Head of Clinical Research at *Imagine*.

Imagine’s clinical research department supports rare disease reference centers and clinical departments that come under the purview of Institut *Imagine*. The promotion support team is composed of two project managers involved in setting up and implementing clinical trials; and the investigation support team, clinical research coordinators (CRC), clinical research technicians (CRT) and mobile clinical research nurses (MCRN), involved in the recruiting patients and in carrying out trials in compliance with good clinical practice and applicable regulations. Within the investigation support team, CRCs are integrated into the reference centers for rare diseases (CRMR), working closely with physicians, thereby contributing to the development of clinical research activities, speeding up patient recruitment and promoting clinical research best practice. Fifteen reference centers of the 31 then affiliated to *Imagine* can benefit from this system.

In addition, four mobile clinical research nurses are specifically assigned to all the Institute’s clinical research teams. They take care of patients who are part of the research protocols, liaise between the care teams and the trial sponsors, and take samples for research. In cooperation with the CRMRs, they develop personalized care pathways for children.

In 2020, out of more than 500 clinical studies involving the Institute’s teams, the resources deployed by *Imagine* to speed up activities made it possible to support 60 projects with institutional or industrial aid and to include 423 patients, in areas such as intellectual disabilities, metabolic diseases, rare skin diseases, kidney diseases, developmental disorders, hematology or immunodeficiencies. These projects include the Defidiag project, which aims to develop high-throughput genome sequencing strategies for the genetic diagnosis of patients with intellectual disabilities. This project – supported by Inserm – whose enrolment began in June 2020, has already included 91 patients out of the 108 planned, relying on the clinical investigation resources deployed by *Imagine* (IMRC and CRC).

Finally, in 2020, *Imagine* launched a joint call for proposals with the Hôpital Necker-Enfants Malades relying on the pooling – for the benefit of the Necker campus CRMRs – of donor funding from the *Imagine* Institute and the Groupe Hospitalier Necker AP-HP. The objective of this call was to encourage the development of collaborative and interdisciplinary projects in the field of clinical research applied to rare diseases, the eligibility criterion being involvement in the project of healthcare teams and patient associations. 15 projects were presented and 4 of them were selected for funding in 2021.

> *“Without the financial resources and clinical research staff provided by the* Imagine *Institute, we would never have been able to conduct this study. Thanks to* Imagine*, we now have the largest cohort of adolescents followed up for the Pierre Robin syndrome in France. It is a rare genetic disease characterized by oro-facial malformations and neonatal sucking-swallowing and breathing problems. The study is now complete, and publication is ongoing.”*
>
> Prof. Véronique Abadie, Head of the General Pediatrics Department at the Hôpital Necker-Enfants Malades and Head of the Reference Centre for Rare Diseases for “Pierre Robin’s Syndromes and Congenital Sucking and Swallowing Disorders” (SPRATON)

The health crisis that marked the year required adaptation and creativity in research laboratories, and the same held true for clinical research teams. The Reference Centers for Rare Diseases maintained consultations and clinical studies as much as possible during and after the first lock-down to waste as little time as possible for patients, and so as not to slow down the development of studies and the recruitment of new patients in them. In addition to these studies, clinical research staff were highly involved in the protocols and studies put in place very quickly to combat Covid-19, and clinical research nurses were very much involved in the field. *“The promotional support team was able to contribute to the rapid implementation of a global study of myocardial and pulmonary disease by MRI and CT in children with COVID-19,”* says Dr Francesca Raimondi, head of pediatric cardiac imaging activity by MRI and cardiac CT at the Hôpital Necker-Enfants Malades AP-HP, which is coordinating the study. To date, more than 120 patients have been enrolled in several countries (USA, Europe, UK, South America). It is the only global registry in the field.

Reference Centers for Rare Diseases at the heart of care

A reference center brings together the strengths of highly specialized hospital teams with proven expertise in a rare disease or group of rare diseases. This medical team covers paramedical, psychological, medico-social, educational and social skills, and organizes patient care in conjunction with all the health professionals concerned.

Of the 34 Rare Disease Reference Centers at Hôpital Necker-Enfants Malades AP-HP, 31 are now affiliated with the *Imagine* Institute. They are the contacts for patient associations, playing a crucial role in the development of clinical trials and the creation of cohorts, without which research could not be conducted. They facilitate the diagnosis and treatment of patients, coordinate clinical research work and help patients to understand more clearly the pathologies. Beyond research, they take into account all facets of a child, considering them a person, not just a disease, guiding them through the transition to adulthood.

31 Affiliated Reference Centers for Rare Diseases

NEPHROLOGY

L. Heidet
Hereditary Kidney Disease in Children and Adults (MARHEA)

A. Servais
Thrombotic microangiopathies (MAT national research center – CNR)


B. Knebelmann & O. Boyer
Idiopathic nephrotic syndrome (INS)

NEURODEVELOPMENT

N. Bahi-Buisson
Intellectual disabilities of rare causes – multiple disabilities

D. Brémond-Gignac
Rare ophthalmological diseases (OPHTARA)

JP Bonnefont
Mitochondrial diseases from child to adult (CARAMMEL)

P. De Lonlay
Metabolic hereditary diseases

I. Desguerre
Neuromuscular diseases
Nord/Est/Ile de France regions.

R. Nabbout
Rare epilepsy (CRéER)

M. Rio
Intellectual disabilities of rare causes

HEMATOLOGY

A. Harroche
Pediatric hemophilia

O. Hermine
Mastocytoses (CEREMAST)

M. de Montalembert
Major sickle cell syndromes, thalassemia and other rare red blood cell and erythropoiesis disorders

IMMUNOLOGY-INFECTIOLOGY-GASTROLOGY


A. Fischer & N. Malhaoui
Hereditary immune deficiencies (CEREDIH)

F. Ruemmele
Rare digestive diseases (MARDI)

P. Quartier dit Maire
Inflammatory rheumatism and rare systemic autoimmune diseases in children (RAISE)

DEVELOPMENT AND CARDIOLOGY

V. Abadie
Pierre Robin syndrome and congenital sucking and swallowing disorders (SPRATON)

J. Amiel
Developmental anomalies and malformative syndromes in the Ile-de-France region (Greater Paris)

D. Bonnet
Complex congenital heart defects (M3C)

D. Bonnet
Hereditary or rare cardiomyopathies and arrhythmias

C. Bodemer
Rare diseases of the skin and mucous membranes of genetic origin (MAGEC)

V. Cormier-Daire
Constitutional bone diseases (MOC)

C. Crétolle
Rare anorectal and pelvic diseases (MAReP)

F. Denoyelle
Rare ENT malformations (MALO)

A. Hagège
Inherited cardiomyopathies and arrhythmias

S. Marlin
Genetic deafness

A. Picard
Clefts and facial malformations (MAFACE)

M. Polak
Rare gynecological diseases (RGD)

K. Wahbi
Cardiomyopathies of neuromuscular diseases Nord/Est/Ile de France

2 CIC (CLINICAL INVESTIGATION CENTERS)

Jean-Marc Tréluyer
Multi-thematic mother and child center (CIC)

Marina Cavazzana
Biotherapies (CIC-BT)

7 AFFILIATED CLINICAL DEPARTMENTS

Pierre Quartier dit Maire
Pediatric immunology, hematology and rheumatology

Olivier Hermine
Adult hematology

Marina Cavazzana
Innovative therapies

Fédération de Génétique Médicale [Federation of medical genetics]

Christophe Legendre
Adult kidney transplant

Rémi Salomon
Pediatric nephrology

Olivier Lortholary
Infectious and tropical diseases

Opening up to society and the Human and Social Sciences

Commonly associated with multiple disabilities, these genetic diseases open up lots of issues about the place of sick people in our societies, as well as the means to be implemented to both live together, with the disease, with the family, and well beyond. *"Supporting families with disease is one of the missions of Institut* Imagine, explains Laure Boquet, General Delegate of the Institute and co-head of the Human and Social Sciences program at *Imagine*. *"The aim is to improve the life course of patients and their loved ones, from diagnosis to treatment and follow-up; and to reflect on the consequences of the disease."*

In 2019, *Imagine* funded a call for proposals launched to improve patients' quality of life. 3 winners were selected, on projects covering the linguistic, sociological and psychological fields. Among them, Stéphanie Smadja, lecturer in linguistics and stylistics at the Université de Paris, Célia Crétolle and Giulia Disnan, respectively coordinator and clinical psychologist of the reference center for rare anorectal and pelvic malformations at the Hôpital Necker-Enfants Malades AP-HP, study the inner voices of children with anorectal, rare pelvic and/or medullary malformations and those of their entourage to find out the ideas they form of these malformations. The other two projects, led by Dr Sandrine Marlin, coordinator of the reference center for genetic deafness at Hôpital Necker-Enfants Malades AP-HP, member of the embryology and genetics laboratory for malformations at *Imagine*, and Prof Rima Nabbout, coordinator of the reference center for rare epilepsy (CRéER), and member of the translational research laboratory for neurological diseases at *Imagine*, are dedicated to transmission and inheritance in young people with genetic deafness and the impact of early and preventive medical monitoring in tuberous sclerosis complex.

Thanks to the Innogrant funding program of Institut *Imagine* Audrey Brugnoli holds a PhD in design and health at the Sciences Arts Création Recherche laboratory at Université PSL. The aim of its "Les Peaux Ethiques" [Ethical Skins] project is to develop new sensitive surfaces to compensate for the loss of sensation associated with certain skin diseases and help patients get back in touch with their skin organs in a positive way: to live "with" and not "despite" this physical disability.

Theater play by the Duruy high school

At the beginning of the year, always keeping the improvement of patients' quality of life in mind, *Imagine* installed a sensory wall in the atrium, where patients come for a consultation. In partnership with the association, It Is Now, and the collective of artists, Dany Rose Studio, this wall offers a fun and joyful time for patients thanks to a visual and sound work that captures, transcribes and amplifies movements in color. *"We were keen to bring together contributive and artistic energies that go beyond the lab bench and care. It is a source of inclusion, sharing and wonder because children develop very moving artistic abilities on their own,"* says Laure Boquet, managing director of the Institute.

At the same time, *Imagine* continued its commitment to international and national programs dedicated to rare and genetic diseases, and alongside patient associations, even though, this year, many events had to be cancelled.

Sensory wall

Raising public awareness

Although access to the Institute was restricted for part of the year, *Imagine* was still able to open its doors for Rare Diseases Day on 29 February 2020. A few hundred visitors discovered the Institute through visits, talks, guided tours and meetings with young researchers. Before that, on 26 February, the Institute engaged in raising public awareness and informing them on the theme of the diagnosis of genetic diseases via a Facebook Live session.

On 28 February, an exceptional cinema club took place in the auditorium of *Imagine* with the screening of the film "Freaks" by Tod Browning (1932). To better understand the daily lives of people suffering from rare diseases and to offer a different perspective on differences, this projection was followed by a debate led by Prof. Stanislas Lyonnet, director of *Imagine*, with Serge Bromberg, film director, and cinema historian, Frédéric Worms, philosopher, professor of contemporary philosophy at the École Normale Supérieure (ENS), assistant director of the Arts at ENS Ulm, member of the National Advisory Committee on Ethics, and Dr. Geneviève Baujat, geneticist at the Hôpital Necker-Enfants Malades AP-HP and *Imagine*.

On 25 February, the Institute also welcomed 130 young 3rd graders (aged 14/15) from the Collège-Lycée Duruy in Paris for a play promoting social inclusion for young people suffering from rare genetic diseases.

As it was unable to open its doors to the public in October, the Institute offered a virtual video tour at the Fête de la Science (Science Festival) on 12 October.

COMMITING

TO THE RACE AGAINST COVID-19

"From the start of the pandemic, Imagine's teams have been committed with incredible responsiveness and immense solidarity, whether in research on the disease, in hospitals offering support in emergency critical clinical care units, through technological and medical innovations, assisting with the set-up of regional testing platforms, or through their support to keep the Institute going throughout this crisis. And our laboratories have been immensely involved in helping to understand and treat serious forms of viral disease, which illustrates once again that research against genetic diseases has implications beyond these diseases".

Prof. Stanislas Lyonnet,
Director of Institut *Imagine*

"We reply on you! Well done to the researchers, doctors, technicians and all Imagine *personnel working on the front of Covid-19. You have been able to adapt, react very quickly, and do everything possible to combat this pandemic,"* says Teddy Riner, sponsor of *Imagine*, in May 2020.

Not only have *Imagine*'s doctors and researchers adapted to the restrictions imposed by Covid-19, many of them have also taken up the fight against this pandemic.

Several teams launched into research to better understand Covid-19

Given their expertise and know-how, five laboratories and four platforms at Institut *Imagine* have used their knowledge of genetic diseases to try to better understand Covid-19, some aspects of which are reminiscent of certain abnormal immune reactions that they have already studied in other circumstances, and to identify genetic factors that predispose some to serious forms, particularly in younger patients.

Several teams immediately responded to the call from the National research agency (ANR) to bring in scientific communities on the pandemic, the Flash Covid-19 call. Two projects involving four *Imagine* laboratories were selected for this call for proposals.

This is how the GENCOVID project was launched, led by the human genetics laboratories for infectious diseases run by Laurent Abel and Jean-Laurent Casanova at *Imagine*, with the aim of identifying monogenic defects in immunity that could be responsible for severe forms of Covid-19 in previously healthy patients. In just a few days, Jean-Laurent Casanova created the Covid Human Genetic Effort Consortium with an American researcher to coordinate forces internationally, with more than 45 sequencing centers and nearly 150 partner institutions worldwide. And, less than six months later, the results were there with two crucial discoveries on severe forms of Covid-19 (see box on page 26)!

At the same time, Frédéric Rieux-Laucat, director of the Immunogenetics of pediatric autoimmune diseases laboratory, in collaboration with Prof. Benjamin Terrier, doctor at Cochin hospital, and Mickaël Ménager, Director of the Laboratory of Inflammatory Responses and Transcriptomic Networks, developed the AIROCovid19 project. By seeking a molecular signature for severe forms of Covid-19, and using single-cell analysis of gene expression, they were able to decipher the deregulated mechanisms leading to hyperinflammation, with the aim of uncovering a signature for severe forms of the disease, with the biological warning signs that could indicate patients at risk of developing acute respiratory syndrome, and thus be able to anticipate the progression of the disease and identify therapeutic pathways. Here too, major advances have been made (see box on page 26).

Team of Laurent Abel and Jean-Laurent Casanova

Following the work carried out by the teams of Laurent Abel and Jean-Laurent Casanova, a 3rd research project was funded by the ANR in December 2020. AABIFNCOV, coordinated by Aurélie Cobat in human genetics laboratories for infectious diseases, is studying the genetic and immunological bases of autoantibodies (autoAc) directed against type-I interferons that predispose patients to severe forms of Covid-19.

The platforms of Institut *Imagine* have also been strongly involved in helping the scientific and medical community to study and better understand the virus. The Data Science platform, led by Nicolas Garcelon, was, for example, called upon by AP-HP to co-coordinate with other hospitals and teams of data scientists, the "COVID - automatic language processing" group. Their project created a database containing clinical information from patients with Covid-19 and from medical reports, to enable researchers and physicians to better understand the disease and its risks associated with disease progression. In a publication in *J Med Internet Res,* the team showed that the use of calcium channel blockers is associated with a decrease in hospital mortality in patients infected with Covid-19.

Imagine and the Hôpital Necker-Enfants Malades AP-HP have also launched the global study "COPID19" to understand the clinical presentation and developments of Covid-19 in patients with primary immune deficiencies, so they can determine the clinical, radiological profile and risks associated with the progression of the disease in these patients at high risk of infection; the project is being conducted with the support of the Data Science platform and the *Imagine* clinical research team.

Mickaël Ménager's team

In terms of hospital care, Prof. Olivier Hermine, hospital practitioner and head of the adult hematology department at Hôpital Necker-Enfants Malades AP-HP, director of the laboratory for cellular and molecular mechanisms of hematological disorders at *Imagine*, is coordinating the CORIMMUNO-19 project launched by AP-HP to conduct randomized controlled trials of drugs, particularly immuno-modulators, in patients hospitalized for Covid-19 infection, with the aim of determining whether certain molecules could prevent patients with a moderate or severe form of the disease from ending up in intensive care, and to speed up treatment and discharge for patients in intensive care. A first trial of the drug Tocilizumab delivered its first results in the CORIM-MUNO-TOCI-1 trial. A publication in *JAMA Intern Med* confirmed that using it helps stop patient's condition from deteriorating so patients with moderate and severe Covid-19 do not end up in intensive care.

And if there is one thing that this crisis has highlighted once more, it is the link and complementarity between research and hospitals, between experimental research and treatment of a disease, which are of mutual benefit to the progress of both. *"The urgency of this situation should not make us forget the fundamentals of research. We continue to carry out research the way we learned to, by coming up with hypotheses, studying them experimentally and rigorously interpreting these results. Time for emergency and time for research must cohabit and move forward together. And it is thanks to solid research structures such as the* Imagine *Institute, associated with AP-HP, that we can meet this challenge by combining experimental rigor, methodological imperative, and speed,"* says Quentin Philippot, PhD student at *Imagine* and intensive care doctor at the Tenon AP-HP hospital.

"The research and care projects launched with incredible responsiveness by our teams continue to produce great results. This work represents a huge step forward in research, screening and the care of patients affected by Covid-19. It is a superb example of the intellectual and operational agility of a hospital university institute capable of making discoveries for all when it is searching for a few. These discoveries once again illustrate that research on genetic diseases, even rare ones, has a direct impact on much more common diseases by adding to general scientific knowledge and hence the understanding of the mechanisms involved," says Prof. Stanislas Lyonnet, Director of Institut *Imagine*.

The importance and quality of this work and these discoveries were welcomed by the French President, Emmanuel Macron, the Minister of Higher Education and Research, Frédérique Vidal, and the Minister of Solidarity and Health, Olivier Véran, during an official visit to Institut *Imagine* on 4 December 2020. And the two discoveries by Jean-Laurent Casanova and Laurent Abel, on the role of type-I interferons in severe forms of Covid-19, and the exceptional presence of autoantibodies in more than 15% of patients with severe forms, were selected from the ten major discoveries of the year by the most renowned scientific journal: *Nature*.

The French president, Emmanuel Macron, visits Institut *Imagine*

Dr. Laurent Abel

THE ROLE OF TYPE-I INTERFERONS IN COVID-19 - 3 MAJOR DISCOVERIES

QUESTIONS TO LAURENT ABEL, JEAN-LAURENT CASANOVA, AND FRÉDÉRIC RIEUX-LAUCAT

Which patients will develop a serious form of Covid-19? Why does the reaction to the infection vary so much from one individual to another? These three researchers began to answer these questions, which are essential for patient care and prognosis. Their findings were published in the leading international scientific journal *Science* in July and September 2020.

You discovered an interferon deficiency in patients presenting with a severe form of Covid-19. What does this mean for understanding the disease and for treatment?

Frédéric-Rieux-Laucat : Our team, in collaboration with teams from AP-HP, Inserm, Université de Paris and the Institut Pasteur, has identified a unique and unexpected immunological phenotype in patients suffering from severe forms. They had a type-I interferon deficiency (IFN type I), molecules of the immune system that fight viruses, associated with a persistent viral load in the blood and an excessive inflammatory response. This type-I IFN deficiency is a signature of serious forms of the disease and could help identify a high-risk population.

Is this type I IFN deficiency the result of two mechanisms that explain at least 15% of severe forms of Covid-19?

Jean-Laurent Casanova : Together with our Franco-American team at *Imagine* and Rockefeller University in New York, in association with the international Covid Human Genetic Effort consortium, we identified the first genetic and immunological causes that explain at least 15% of serious forms of Covid-19. The patients all have one thing in common, which confirms the crucial role of type-I IFN in the immune response against the virus: they have a defect in the production or activity of type-I interferons.

Laurent Abel : But the mechanisms behind this dysfunction differ. For 3 to 4% of severe forms, we identified genetic abnormalities in a group of genes already known to govern the immune response controlled by type-I IFN against the influenza virus, resulting in reduced production of type-I IFN. In 10 to 11% of other patients with severe forms, we identified autoantibodies that block the action of type-I IFN and neutralize their effect. These autoantibodies were detected primarily in men and people over 65 years of age.*

Impaired type-I interferon activity and inflammatory responses in severe COVID-19 patients
Jérôme Hadjadj et al. - *Science*, 13 July 2020

Inborn errors of type I IFN immunity in patients with life-threatening COVID-19
Qian Zhang et al. - *Science*, 24 September 2020

Autoantibodies against type I IFN in patients with life-threatening COVID-19
Paul Bastard et al. - *Science*, 24 September 2020

* At the time of writing this report, the teams of Jean-Laurent Casanova and Laurent Abel started working with Cerba HealthCare, a leading player in medical diagnosis, to develop the clinical applications of these discoveries, and to screen people at risk of developing a serious form so their treatment could be adapted accordingly.

Share knowledge to move faster

In general, and especially within the context of this pandemic, passing on, discussing and sharing ideas and discoveries are essential to ensure scientific progress. *Imagine* scientists and physicians involved in Covid-19 research have, therefore, been very active in disseminating their findings and knowledge to the French and international scientific and medical community as well as to the general public.

The Institute's researchers took part in scientific seminars and gave lectures on Covid-19. For example, Alain Fischer, first director of Institut *Imagine* dedicated his final lesson at the Collège de France in June to the immune response to Covid-19. Frédéric Rieux-Laucat, laboratory director at *Imagine*, gave a lecture at the Festival des nouvelles explorations [New explorations festival] in September on genetic research on Covid-19, its treatment, its disciplines and cooperative projects to conduct this research. Also in September, Laurent Abel and Jean-Laurent Casanova, laboratory directors at *Imagine*, held a press conference to explain their findings on the serious forms of Covid-19. Alain Fischer and Jean-Laurent Casanova also participated in October in the S3 Odéon dedicated to Covid-19 and what science says about it, with two talks entitled "Can research save us?" and "How can we treat severe forms?".

Doctors and researchers have used the media and social networks to provide scientific and factual insight, thus enabling a better understanding of the virus and the challenges of research. Among them, Prof. Jean-Laurent Casanova, appointed member of the National Scientific Council on Covid-19 established by the Minister of Health at the request of the French President, spoke to the media to explain the disease and related scientific knowledge. Prof. Alain Fischer, appointed head of the National Steering Committee on Vaccine Strategy, worked to demonstrate the benefits of vaccination in the fight against the pandemic and to explain its implementation.

Prof. Jean-Laurent Casanova

Dr Frédéric Rieux-Laucat

Doctors and researchers working on the hospital front

Some medical researchers went back to work in hospital wards during the crisis, to help in emergency and intensive care departments on our campus and in the Ile de France region.

For example, Quentin Philippot, a doctoral student in the laboratory headed by Jean-Laurent Casanova and Laurent Abel, who had just finished his internship in intensive care and pneumology, joined the intensive care department of the Tenon AP-HP hospital. *"I immediately felt concerned about the Covid-19 crisis and wanted to help as soon as possible,"* he said. *"What really differed from our normal work, and what was most difficult, was on the one hand the volume and severity of the patients' condition, and on the other hand the isolation of these patients from their families. I very much admire the immense solidarity that has been expressed and the high quality of the public hospitals where all staff offered to help without hesitation,"* he says.

Marie-Louise Frémond and Alice Lepelley

Julien Zuber

"The extraordinary involvement of everyone in this crisis is to be applauded," confirms Julien Zuber. This nephrologist specialized in kidney transplantation, professor of immunology at the Université de Paris and researcher in the human lymphohematopoiesis laboratory of Isabelle André in *Imagine*, has massively increased her hours working at the Hôpital Necker-Enfants Malades AP-HP. *"Treating Covid-19 patients is physically and psychologically stressful, so we took it in turns working in intensive care. I also helped to quickly set up remote consultations for the follow-up of transplant patients with whom the link could not be broken."*

Marie-Louise Frémond, pediatrician at the Hôpital Necker-Enfants Malades AP-HP and postdoctoral fellow at the neurogenetics and neuroinflammation laboratory, headed by Yanick Crow at *Imagine*, wanted to play her part through taking emergency calls and remote surveillance of patients, to *"do my bit and be involved in this new mutual assistance and volunteering systems, which, I think, will help defeat this pandemic"*.

The clinical geneticists of the *Imagine* Institute and the Hôpital Necker-Enfants Malades AP-HP have, for their part, helped massively to keep up the link between intensive care staff and families of patients with Covid-19. At the time of writing this report, they are also involved in vaccinating campus staff.

Solidarity initiatives to help fight the pandemic

3D printer fleet – Hôpital Cochin AP-HP

Faced with this crisis, exceptional initiatives have emerged in addition to these direct actions to support hospitals.

Imagine, with Dr. Roman Hossein Khonsari, a researcher at the Molecular and Physiopathological Bases of Osteochondrodysplasia laboratory, run by Laurence Legeai-Mallet and Valérie Cormier-Daire at *Imagine*, participated in the "3D COVID" project for 3D printing of medical devices for hospitals. In partnership with the Université de Paris, the start-up Bone3D, the AP-HP, and with financing from the Kering group, a fleet of 60 3D printers was set up at the Hôpital Cochin AP-HP to meet the specific and critical needs of medical equipment in the first weeks of the pandemic. *"This sort of internal factory has made it possible to meet the urgent needs of AP-HP and Ile-de-France hospitals by producing, in 48 hours, protective goggles and visors for the face, valves, seals and parts for emergency artificial respirators, intubation equipment, handles, syringe pumps etc.,"* he explains.

And because the fight against Covid-19 requires first and foremost testing, Olivier Gribouval, a research engineer in the Hereditary Kidney Disease laboratory, run by Sophie Saunier at *Imagine*, and a group of volunteers from other institutions, set up and developed the COVID-19 Ile-de-France platform. Created with the General Directorate of Health and AP-HP, its aim is to increase the capacity of RT-PCR screening tests, first with a view to ending the lock-down in May, then throughout the pandemic. *"We built this platform in 3 weeks and started the first phase of intense screening at the end of April, and since then we have been taking turns with staff and volunteers to help,"* says Olivier.

The institute also donated blouses and masks to Hôpital Necker-Enfants malades AP-HP at the start of the health crisis.

All Institute staff mobilized

And all these actions and advances have been possible thanks to the commitment of all the Institute's staff, who have worked together to keep *Imagine* operating during the lockdowns and organize the return to work and ensure its continuation in complete safety. This collective, which allowed *Imagine* to keep its scientific work at a high level, in an unprecedented situation and in conditions never before encountered, is the pride of the Institute.

The safety of everyone at all times is a priority that has guided the actions and considerations of the Institute since the start of the pandemic. It is a major project, run by our General Delegate Laure Boquet, and which has required many issues to be taken into account and constant adaptation. Several teams were involved, with, on the front line, the health, safety and environment department, the internal departments, the Institute's accident prevention assistants (AP) and L2/L3 representatives, the management, the operations department, the legal department, the HR department, communication, laboratory directors, platforms and services, as well as a group of volunteers.

Moussa Sy

"It is during these moments that we see* Imagine *as a whole, in its unity! I am proud to have participated in preparing the Institute for its reopening in May, and I am continuing this group work to ensure that research and care activities is pursued throughout this crisis".

Bruno Estebe, engineer and accident prevention assistant at *Imagine*.

"The most complex thing about reopening the Institute in May was acquiring personal protective equipment and hydro-alcoholic solutions, because the demand was higher than supply. The preparation of the business recovery plan was a real adventure, with a great feeling of solidarity on the part of the teams," recalls Cécile Bureau, Head of Internal Services. *"Since the beginning of the Covid-19 crisis, we have been on alert. Being confronted with a new risk for everyone, and having to deal with it, is complex and pushes everyone to their limits. The accident prevention assistants and HSE representatives, as well as the L2/L3 representatives immediately responded and were of great help. All these people have been incredibly supportive even from a distance,"* adds Anne-Marie Laurencine, Health, Safety and Environment Coordinator.

"This group work, the exemplary involvement of all staff, their mobilization and their initiative, have once again demonstrated the solidarity we have within our Institute. Imagine is first and foremost a story of men and women dedicated to a cause, and this year illustrates that perfectly. So, everyone, whether inside or outside the walls, has allowed Imagine to keep going during this crisis of unprecedented brutality, and then to open up again with unparalleled agility," says Laure Boquet, General Delegate of *Imagine*.

Imagine's friends and donors, loyal and by our side

Many of *Imagine*'s friends have come forward since the health crisis began to express their support for the Institute so it continues to operate, and so science and care can move forward in the best possible way.

To allow the Institute's staff to resume their activities safely when it reopened in May, generous donations were made to *Imagine*. For example, the LVMH group donated 6,000 masks and 1,500 tubes of hydroalcoholic solution, and the 3D printer company donated 450 door handles printed in 3D. The Accord Group provided *Imagine* staff with parking spaces at its Novotel Montparnasse so they could come by car when business resumed in May and June 2020. Pharmacy Pharmavance Escudier donated 2,000 surgical masks.

From the Institute's sponsor, Teddy Riner, to the president of its International Scientific Council, Liz Blackburn, to its loyal donors and friends, messages of encouragement and support poured in.

"From my tatami, I have been at your side in the battles that you are fighting with so much talent and energy, against Covid-19 and genetic diseases. As always, you have my full confidence and support."

Teddy Riner, sponsor of *Imagine*, April 2020

"Your group and individual contributions, in many ways, are more important than ever, and I would like to send you my best wishes and hopes as we all strive to get out of this pandemic."

Liz Blackburn, President of the *Imagine* International Scientific Council, May 2020

"Knowing that teams from Imagine *are working to come up with ways to find a solution to this Coronavirus is no surprise. Her researchers put all their talent into unravelling the mysteries of this new disease. If they find them, great; if not, others will find them. And for us – and it's the most important thing – knowing that the best people are collectively committed to this battle. And victory will in any case only come by working together".*

Sébastien de Lafond, co-founder of MeilleursAgents, great friend and supporter of *Imagine*, May 2020

THINK OF THE FUTURE

"The crisis that we have experienced and are still going through together is pushing us ever more to think about the future in an innovative and pioneering way. The challenges we face and expect are numerous, exciting and pivotal. Like any crisis, this terrible pandemic also has the benefit of revealing unsuspected forces: incredible solidarity, formidable scientific reactivity, and inventiveness, both medical and industrial. In this area too, by practicing the best science today, Imagine *is inventing the best medicine of tomorrow to meet the expectations of families and patients and give them hope".*

Prof Stanislas Lyonnet,
director of the *Imagine* Institute

2020 was a singular year in many ways, but *Imagine* has not forgotten to look ahead to prepare for the future, anticipate major developments in research and care, and to continue to put innovation at the heart of its projects.

Continuing to innovate

Initiate, protect, develop, transfer

Imagine, with the support of its Innovation and Technology Transfer Department "DIVA", has since its creation demonstrated its ability to accelerate translational and clinical research efforts, and to promote these developments to socio-economic partners.

With a view to industrial transfer, one of the first steps is to protect scientific results – firstly by filing a patent. In 2020, ten new patents were filed within the Institute. The *Imagine* patent portfolio covers a very broad spectrum of applications and includes 57 active patent families. These patents and other expertise developed at *Imagine* have already resulted in the signing of 12 operating licenses. Many developments are conducted in partnership with companies in order to more effectively ensure the industrialization and marketing stages necessary to disseminate advances for the benefit of patients. In 2020, despite the global health crisis, many partnerships continued (for example with QED in the field of achondroplasia, STEP Pharma in immunology/oncology, Cellectis in hematology, etc.) or were established – for example with the medical analysis laboratories CERBA Healthcare in the development of a predisposition test for severe forms of Covid-19, or with the start-ups AtmosR and Medetia in the field of Ondine syndrome.

All the industrial contracts in force in 2020 generated more than five million euros in revenue, invested in the Institute's research and care work. Some projects give rise to the creation of start-ups: since 2012, ten start-ups, including seven resulting from *Imagine* research, have been created. Five of them were initiated during the *Bioentrepreneurs* program, whose aim is to train entrepreneurs and accelerate projects for healthtech start-ups. At the end of 2020, more than 400 therapeutic or diagnostic solutions were being developed, from preclinical to clinical – 106 of them directly resulting from the research work of the Institute's laboratories.

Website dedicated to manufacturers

To generate new collaborations, in June 2020, *Imagine* launched a website dedicated to the industrial community, which lists the Institute's preclinical and clinical resources, expertise and partnership opportunities, presented by therapeutic area and pathology or group of pathologies. It offers an overview of cell and animal models, patient samples and cohorts, know-how and patents accessible in laboratories, reference centers, clinical services and technological platforms.


Team led by Laurence Legeai-Mallet and Valérie Cormier-Daire

To give additional impetus to the most innovative projects, *Imagine* has set up three internal funding programs.

The Crosslab program is a system for initiating cross-cutting projects involving several laboratories, reference centers and platforms of the Institute. Five projects have been launched since the creation of the program in 2017, involving 14 laboratories, 7 rare disease reference centers and around ten technological platforms. *"It is a crucial program for developing cross-functionality within the Institute, generating breakthrough innovations. The teams are also encouraged, and helped to do so, to raise additional external funding with a view to even larger projects,"* says Romain Marlange, Director of the Innovation and Technology Transfer Department.

The Innogrant program is focused on technology transfer. Its purpose is to promote or support therapeutic or diagnostic innovation projects. It directs these projects towards the first stages of development and proof of concept. Since its launch in 2018, it has enabled the emergence of six projects, one of which led to the creation of a start-up in the field of digital health, and two are being supported as part of the Springboard accelerator, in the fields of biotechnologies and medical technologies.

Finally, **Springboard** is a system for accelerating projects aimed at creating start-ups, by providing large-scale financing and high-level industrial and entrepreneurial expertise. Launched in March 2020, it has already supported 3 initial projects (see below).

Institut Carnot labelling, giving value to research in genetics

In February 2020, the *Imagine* Institute was given "Institut Carnot" label. Obtaining this label illustrates the quality and dynamism of industry and partnership relations of Institut *Imagine* and their recognition by the Ministry of Higher Education, Research and Innovation. This labelling provides additional funding for partnership research activities. As Stanislas Lyonnet, Director of Institut *Imagine* pointed out, *"an important step has just been taken in the development of Institut* Imagine *with the obtaining of Institut Carnot label. The promotion of our research work and the mobilization of industrial partners are essential to bring life-changing innovations to patients with rare genetic diseases as quickly as possible. Just a few months after the extension of our university hospital institute accreditation for five more years, granted by the Prime Minister and the SGPI, – General Secretariat for Investissement – Imagine now has the two accelerators necessary for its development: the best science of today for the best medicine of tomorrow with IHU label, and the best promotion of research with Carnot label".*

Springboard, a pioneering and unique initiative in the field of genetic diseases

Imagine launched "Springboard" in 2020, the first financial and expertise accelerator dedicated to genetic diseases. Springboard is an accelerator program for upstream projects with strong potential for transfer in the therapeutic, diagnostic and care field, for the benefit of patients, primarily via the creation of start-ups. *"One of the critical stages in the transformation of scientific results into innovation is the so-called proof-of-concept phase: before this stage, the results available are still often too preliminary and fragmentary to attract all the necessary investments. This is where the Springboard accelerator comes in,"* explains Romain Marlange, Director of the Innovation and Valorization Department. This scheme involves very high-level scientific and industrial experts via the Scientific and Investment Committee and a network of experts and supports selected projects up to the stage of maturity required to attract investors or industrial companies. Apart from achieving research results in diagnostic and therapeutic solutions, it creates economic value, which is reinvested over time into the Institute's research activities.

From this first year, three projects have benefited from this program, in areas as varied as the development of natural extracts in the treatment of achondroplasia, the most common form of dwarfism, 3D visualization of organs for surgical planning purposes, as well as for the development of a gene therapy strategy for certain forms of B-cell lymphoma. These projects could lead, within 12 to 24 months, to the creation of start-ups that will change the lives of patients.

Major cross-cutting projects awarded national programs

In 2020, *Imagine* was awarded or has coordinated the launch of two major cross-cutting projects supported by the government and the National Research Agency (ANR) as part of the Investissements d'Avenir program (PIA).

In November 2020, the **MedTech Generator & Accelerator** consortium was awarded the SIA program (SATT-incubators-accelerators) of Investissements d'Avenir program, operated by Bpifrance. Led by the Institut du Cerveau (ICM) with Institut *Imagine* the Institut de la Vision [Vision Institute] and Institut Pasteur, its objective is to develop innovative support programs to accelerate the growth and development of start-ups specializing in health and artificial intelligence in the field of neuroscience, genetic and rare diseases. By pooling the programs to support medtech and deeptech start-ups of partners, it will offer personalized support for researchers wishing to create their own company.

Coordinated by Institut *Imagine* and with funding of 9.9 million euros over 5 years, the **ATRACTion** program is one of the winners of the 4th call for Recherche Hospitalo-Universitaire en santé [Hospital-university health research] proposals of the Investissements d'Avenir program. Launched in 2020, the project aims to develop disruptive and transformative approaches in diagnosis, prognosis and therapies to combat pathologies related to autoimmunity and inflammation mechanisms in primary immune deficiencies. As part of a consortium agreement signed in November 2020, it brings together academic scientific experts from different fields (immunology, microbiology, data sciences, artificial intelligence, multi-omic analyses), doctors and industrial partners. Multiple partners are taking part in this ambitious project: Sanofi, Ariana Pharmaceuticals, Assistance Publique - Hôpitaux de Paris (AP-HP), INRAE, CEA, Institut Pasteur, Institut Curie, Université de Paris, Sorbonne Université and Inserm. *"The strength and originality of this project is to carry out biological analyses at single-cell level, which will lead to the emergence of new biological interaction networks hitherto unsuspected, and to analyze at the same time the composition of the microbiota and microbial metabolites to understand the role of intestinal bacteria in these pathologies,"* announces Dr. Frédéric Rieux-Laucat, project manager.

Frédéric Rieux-Laucat's team

Single-cell analysis for genetic diseases

With regard to innovation in analysis at single-cell level, *Imagine* inaugurated on 14 October, in the presence of Valérie Pécresse, President of the Ile-de-France region, and Pierre-Antoine Molina, Prefect, Secretary General for Public Policies of the Prefecture of the Ile-de-France region, its new platform, the LabTech Single-Cell@*Imagine*. This technological laboratory, equipped in particular with the first new-generation Chromium device in Europe, studies the cells of young patients individually with genetic diseases. This dive into the heart of cells with unprecedented precision gives us a fresh look at genetic diseases.

Within a few years, this technology will allow physicians to include a patient's cellular identity card in clinical data to better identify their disease, their risk of progression, and the best treatment to offer them. Co-funded by the Ile-de-France region as part of the SESAME Filières PIA program, this technological laboratory is open to the academic and industrial community.

Mickaël Ménager

According to his manager, Mickaël Ménager, *"Single-cell analysis is one of the pillars of the growth of truly personalized medicine taking into account the maximum amount of data specific to the individual and their disease. With single-cell analysis, we are changing scale. In single step, we can now analyze the expression of thousands of genes on more than 10,000 cells per individual".*

"With a disease or tissue, each cell can be the seat of different disorders with varying impacts. Thanks to the single-cell analysis, we can look with precision at 15 to 20% of the most expressed genes per cell and the individual characteristics of each cell. And it is that difference in a cell that can sometimes explain the origin of a disease or its response to a treatment. By comparing the cell identity cards of different patients, we could, for example, discover common points between pathologies and choose appropriate treatments," explains Francesco Carbone and Marine Luka, research engineers at *Imagine*.

Francesco Carbone and Marine Luka

Looking forward to the research of the future

Young researchers from Institut *Imagine*

In addition to these advances and progress made in 2020, the Institute was committed to continuing to develop a breeding ground conducive to innovation and future science and research, thanks in particular to the recruitment and training of researchers and doctors.

Three young researchers supporting research at *Imagine*

Young researchers often think of a position at a university, Inserm or CNRS as being the Holy Grail, but competition to get in is tough. This year, three young researchers from the *Imagine* Institute, Emilie Dambroise, Marianna Parlato, and Benedetta Ruzzenente, crossed this milestone, obtaining a position as research fellow at Inserm.

"To succeed, we need a sufficiently mature project," explains Emilie Dambroise, who can now devote herself with less stress way to the research that has been close to her heart since her thesis and consists of identifying the dysregulated physiopathological mechanisms following the modification of the *FGFR3* gene, responsible for craniosynostoses, diseases due to "premature welding" of the skull bones. This poor fusion of the cranial vault has an impact on brain development.

Benedetta Ruzzenente is dedicated to the study of mitochondrial diseases. Her projects include the study of the tissue specificity of diseases related to the mutation of a nuclear gene coding for a mitochondrial protein involved in regulating mitochondrial gene expression.

Marianna Parlato is studying inflammatory bowel disease, which includes Crohn's disease and ulcerative colitis. It affects about 1 in 1,000 individuals in Western countries, most frequently young adults. These inflammatory diseases usually result from a complex interaction of genetic and environmental factors.

"Mitochondrial diseases are very heterogeneous, involving more than 300 genes to date. They are also quite difficult to detect because the clinical signs are often very similar to those observed in other pathologies".
Benedetta Ruzzenente

"It is now recognized that inflammatory bowel disease results from pathological interactions between the microbiota and the immune system in genetically susceptible individuals. I'm trying to better understand why they occur".
Marianna Parlato

Training the researchers of the future

Passing on knowledge and openness are part of *Imagine*'s key missions. Students, researchers, physician-researchers and bioentrepreneurs take part in dedicated training programs that promote the dual skill area of research and medicine that makes the Institute unique and strong. This teaching mission, conducted with the Université de Paris, a founding member of *Imagine*, its doctoral schools, could not develop without the very generous support from the Bettencourt Schueller Foundation, honorary sponsor of the Institute. It supports the *Imagine* seminar center, which contributes to the dissemination of knowledge through the organization of scientific conferences and discussions, and funds some of the training programs by and for research (MD-PhD, Temps protégé, *Bioentrepreneurs Launchpad*).

In the very particular context of 2020, *Imagine* was keen to maintain and even strengthen its student, teaching and knowledge transfer programs. As a result, the Institute continued to take in PhD students. In addition to recruiting doctoral students via French doctoral schools, which allowed students to work in *Imagine*'s laboratories, the Institute has been participating in the Pasteur Paris-University (PPU) program for recruiting international doctoral students since 2020, in collaboration with several Paris universities. No fewer than 152 students applied, proof of the attractiveness of the institute's research laboratories. After a tough selection, 3 students were selected and will carry out their research in one of the laboratories of the *Imagine* Institute, starting in the 2021 academic year.

At the same time, 5 doctors have also benefited from the MD-PhD health and science program, which allows young doctors, pharmacists and odontologists who have already obtained a master's 2 in research to complete their training by completing a science thesis under the supervision of a researcher from a laboratory at *Imagine*. The "Temps protégé pour la recherche" [Protected time for research] program aims to bring clinicians closer to clinical or fundamental research by giving hospital doctors, pharmacists or dentists "protected" time dedicated to their research project. One person was on a protected time contract in 2020. In 2020, 24 students and attendees not enrolled for examinations joined the second session of the *Bioentrepreneurs Launchpad*. Designed in 2016 in partnership with the Université de Paris, HEC Paris and the Ecole Polytechnique,

Tony Fadell visits the Institute

Bioentrepreneurs Launchpad 2020 "Focus Event"

this training program aims to accelerate projects for healthtech start-ups and makes the Institute's network available for future bioentrepreneurs to help them in the early stages of creating their start-ups. Since its launch, it has trained 68 bioentrepreneurs involved in 24 biomedical innovation projects that have led to the creation of 5 start-ups.

On 10 March, Tony Fadell came to meet students to spend some time sharing ideas and discussing issues regarding innovation and entrepreneurship. On 7 October, "Matching Day" took place, a day that brought together over 60 participants to match students up with project sponsors, researchers or doctors proposing biomedical innovation projects. 15 deeptech projects presented by *Imagine* as well as the Institut du Cerveau (ICM), the Institut Curie, the CNRS Innovation, the IMT Lille Douai, AP-HP and by bioentrepreneurs. As a result, the student teams worked full-time (in Q1 2021) on their projects with personalized coaching in partnership with Deeptech Founders.

In addition to these training programs, *Imagine* offers students and young researchers a taste of institute and scientific life, including during the lockdowns that marked the year. Thanks to the actions of the Association des Jeunes Chercheurs d'*Imagine* [*Imagine* young researchers' association] (YR2I), the Association Sportive d'*Imagine* [*Imagine* Sports Association] (ISA), and the Café des post-doctorants (see page 52), they can take part in scientific and social events to forge links and create synergies, as well as organize professional seminars and events, training and support in their careers and integration.

Recruiting new teams and developing expertise

At the end of 2020, Institut *Imagine* launched an international call for tenders for the recruitment of a new research team to work in the field of the genetics of neurodevelopmental disorders. Since its creation, the *Imagine* Institute has recruited 8 new teams, 7 of which are led by foreign or French researchers returning from abroad. In addition, 20% of researchers in *Imagine* teams are international, coming from more than 38 countries.

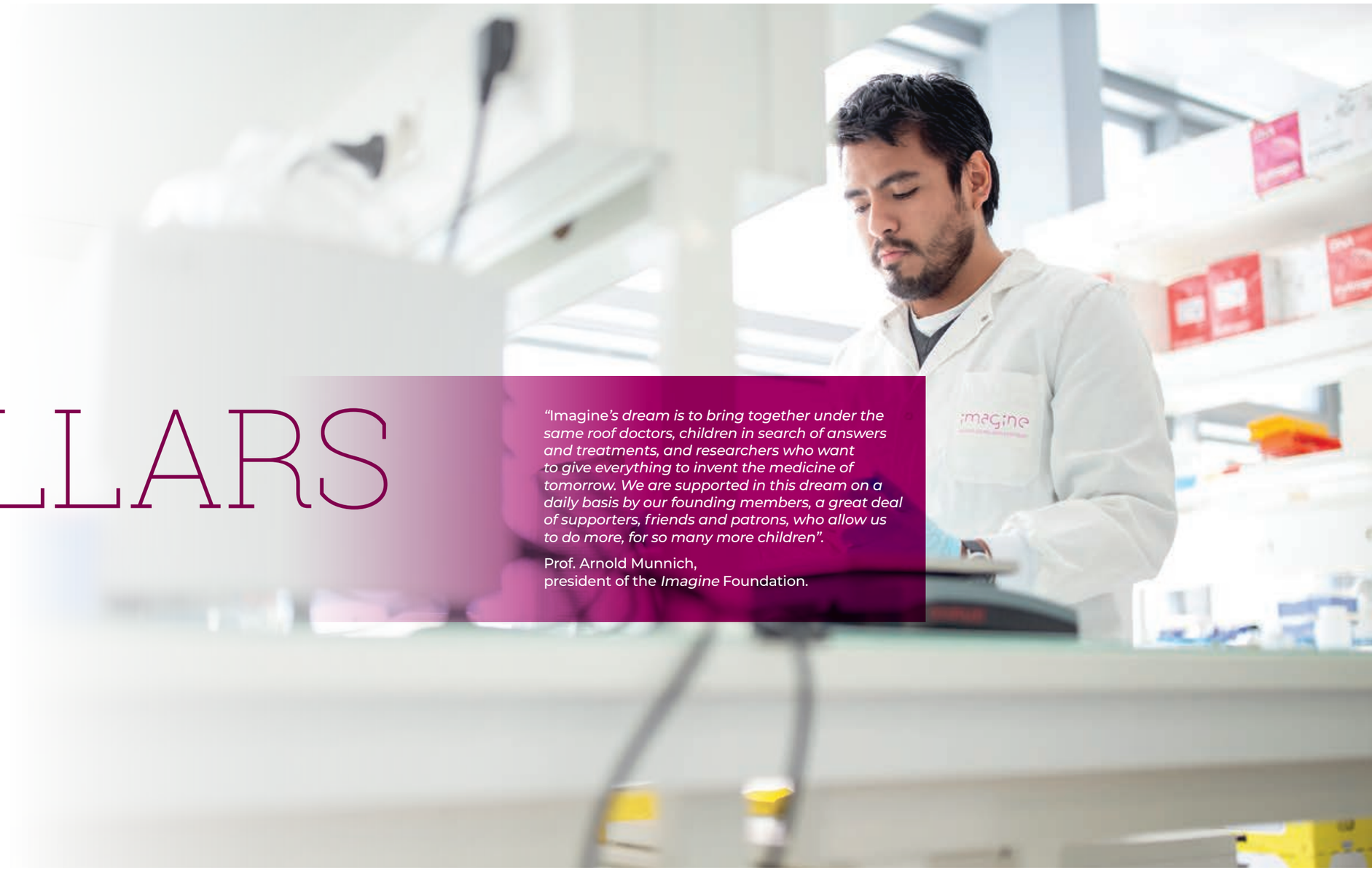
The arrival of new international teams is a way of ensuring a diversity of knowledge, expertise and approaches that contribute to accelerating overall research progress at the Institute. It is also a great opportunity for young researchers to develop their own work. As Annarita Miccio, a young director of the Chromatine laboratory and gene regulation during development, of Italian origin, explains, "Imagine *is the ideal place to develop projects involving doctors and researchers. No other place would have allowed me to progress so quickly in my research and especially in their application for the benefit of patients*".

This new recruitment is part of *Imagine*'s 2018-2028 roadmap (pages 46 - 47), one of the objectives of which is to recruit four international research team leaders by 2028 in order to maintain its level of excellence and continue its international expansion.

OUR PILLARS

"Imagine's dream is to bring together under the same roof doctors, children in search of answers and treatments, and researchers who want to give everything to invent the medicine of tomorrow. We are supported in this dream on a daily basis by our founding members, a great deal of supporters, friends and patrons, who allow us to do more, for so many more children".

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



"If there is one thing that this year 2020 has perfectly illustrated, it is the collective commitment and devotion to the cause of sick children of all Imagine *staff and supporters. More than ever, the Institute has demonstrated its group strength, its spirit of solidarity, and the exemplary involvement of its teams, supporters and friends, always geared towards an objective: to fight genetic diseases for the benefit of sick children and their relatives,"* says Prof. Stanislas Lyonnet, Director of Institut *Imagine*

Research and care teams united with the same aim

***Imagine*'s strength is being able to bring together 24 research teams, 4 associated laboratories of the Hôpital Necker-Enfants malades AP-HP, 17 technological platforms, 31 reference centers for rare diseasesand 7 affiliated clinical units of the Hôpital Necker-Enfants malades AP-HP, with patients at the center. By bringing together all these players, *Imagine* creates the right conditions for going further and faster thanks to a unique "loop" approach: clinical observation, analysis and understanding of the causes and mechanisms of diseases that encourage the discovery of new diagnoses, new treatments and their implementation.**

Changing the lives of families affected by genetic diseases by inventing the medicine of tomorrow

Nearly 8,000 genetic diseases have been recorded so far and new ones are being discovered. In Europe, more than 35 million people are affected, as are almost one in twenty people in France. While 30,000 new people are affected each year in France, more than 50% of these diseases have not yet been diagnosed, and there is no specific treatment to cure 90% of genetic diseases.

To deal with this public health problem, *Imagine* has set itself new ambitions as part of a 10-year roadmap "2018-2028", the objectives of which were adjusted in 2020 after the announcement at the end of 2019 of the extension of accreditation and funding of the Institute's University Hospital Institute for the period 2020-2024 as part of the Investissements d'Avenir (PIA) program.

In 2020, *Imagine* made progress with its objectives:

- To close the diagnostic gap for patients, bringing the diagnostic rate to 80%.
- To double the avenues and research projects on the mechanisms of diseases and double the number of clinical trials, to give access to treatment for 30% of patients and double the therapeutic solutions available.
- To target common mechanisms to treat disease groups.
- To continue to add to number of the Institute's exceptional cohorts, starting points for all research work and future advances.
- To continue its outward looking approach and its scientific resourcing, in particular internationally, through the recruitment of new teams as well as international collaborative projects, and to expand its horizons and actions to take in human and social sciences.
- To invest in technological innovation.
- To accelerate its bioinformatics, genomics and data processing programs.
- To support students and young researchers with structured teaching programs, career support and a mentoring system.

The actions carried out in 2020 to achieve the above aims, include, among others, the call for applications launched in October 2020 for the recruitment of a new international team, the integration of *Imagine* into the teaching program dedicated to international Pasteur-Université de Paris doctoral students, the launch of the Institute's human and social sciences program with the funding of three projects, and many major discoveries in research and care.

Through 6 integrated research and care programs

To achieve the objectives of this roadmap, *Imagine*'s strengths have been focused on six key priority areas for the coming years (see pages 46 - 47). Each of these areas brings together all the dedicated experts, research teams, technological platforms, associated laboratories, reference centers for rare diseases and clinical units.

6 INTEGRATED RESEARCH AND CARE PROGRAMS:

IMMUNOLOGY/ INFECTIOLOGY
Diseases of the immune system and genetic predispositions to infections, which affect 1 in 5,000 children in France.

NEUROLOGICAL AND NEURODEVELOPMENTAL DISEASES
Nearly 3% of children are affected.

HEMATOLOGY
Blood cell disease including the most common genetic disease, sickle cell anemia.

DEVELOPMENT AND CARDIOLOGY
2 to 3% of births are affected by congenital malformations or developmental illnesses.

NEPHROLOGY
More than 150 kidney diseases due to genetic alteration.

A TRANSVERSE ACCELERATION PROJECT:
COMPUTER-ASSISTED DATA SCIENCE AND DECISIONS
Through the development of bioinformatics tools and artificial intelligence, its objective is to make sense of clinical and biological data, to explore areas as yet unknown to accelerate the implementation of tomorrow's medicine.

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

NEPHROLOGY

RESEARCH LABORATORIES

- Hereditary kidney disease ▸ **S. Saunier & C. Antignac**
- Biology and epithelial diseases ▸ **M. Simons**

REFERENCE CENTERS FOR RARE DISEASES

- Hereditary kidney disease in children and adults ▸ **L. Heidet**

CLINIQICAL SERVICES OF THE HÔPITAL NECKER-ENFANTS MALADES

- Nephrotransplantation ▸ **C. Legendre**
- Pediatric nephrology ▸ **R. Salomon**

NEUROLOGICAL AND NEURODEVELOPMENTAL DISEASES

RESEARCH LABORATORIES

- Genetics of neurodevelopmental disorders ▸ **V. Cantagrel**
- Translational research on neurological diseases ▸ **E. Kabashi**
- Genetics and development of the cerebral cortex ▸ **A. Pierani**
- Genetics of mitochondrial diseases ▸ **A. Rötig**
- Ophthalmological genetics ▸ **JM. Rozet**

ASSOCIATED LABORATORIES

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

REFERENCE CENTERS FOR RARE DISEASES

- Intellectual deficits of rare causes ▸ **M. Rio**
- Intellectual disabilities of rare causes – multiple disabilities ▸ **N. Bahi-Buisson**
- Rare eye diseases ▸ **D. Brémond-Gignac**
- Metabolic hereditary diseases ▸ **P. de Lonlay**
- Mitochondrial diseases in adults and children ▸ **JP. Bonnefont**
- Rare epilepsy ▸ **R. Nabbout**

IMMUNOLOGY INFECTIOLOGY

RESEARCH LABORATORIES

- Human genetics of infectious diseases: complex predisposition ▸ **L. Abel**
- Human genetics of infectious diseases: monogenic predisposition ▸ **JL. Casanova**
- Intestinal immunity ▸ **N. Cerf-Bensussan**
- Neurogenetics and neuroinflammation ▸ **Y. Crow**
- Lymphocytic activation and susceptibility to Epstein-Barr virus ▸ **S. Latour**
- Inflammatory responses and transcriptomic networks in diseases ▸ **M. Ménager**
- Molecular basis for immune homeostasis abnormalities ▸ **G. Ménasché & F. Sepulveda**
- Immunogenetics of pediatric autoimmune diseases ▸ **F. Rieux-Laucat**
- Genome dynamics and immune system ▸ **JP. de Villartay & P. Revy**

REFERENCE CENTERS FOR RARE DISEASES

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

CLINIQICAL SERVICES OF THE HÔPITAL NECKER-ENFANTS MALADES

- Pediatric Immunohematology and Rheumatology ▸ **P. Quartier dit Maire**
- Infectious and tropical diseases ▸ **O. Lortholary**

HEMATOLOGY

RESEARCH LABORATORIES

- Human lymphohematopoiesis ▸ **I. André**
- Cellular and molecular mechanisms of hematological disorders and therapeutic implications ▸ **O. Hermine**
- Chromatin and gene regulation during development ▸ **A. Miccio**

REFERENCE CENTERS FOR RARE DISEASES

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

CLINIQICAL SERVICES OF THE HÔPITAL NECKER-ENFANTS MALADES

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

COMPUTER-ASSISTED DATA SCIENCE AND DECISIONS

RESEARCH LABORATORIES

- Clinical bioinformatics ▸ **A. Rausell**
- Department of the Hôpital Necker-Enfants Malades
- Fédération de génétique médicale [Federation of medical genetics]
- Medical Informatics ▸ **A. Burgun**

DEVELOPMENT & CARDIOLOGY

RESEARCH LABORATORIES

- Embryology and genetics of malformations ▸ **J. Amiel & S. Lyonnet**
- Genetic skin diseases: from physiopathological mechanisms to treatments ▸ **A. Hovnanian**
- Molecular and physiopathological bases of osteochondrodysplasia ▸ **L. Legeai-Mallet & V. Cormier-Daire**
- Morphogenesis of the heart ▸ **S. Meilhac**

ASSOCIATED LABORATORIES

- Molecular bases for congenital and neonatal endocrine disorders and new therapeutic strategies ▸ **M. Polak**
- Imag2 Computational anatomy for minimally invasive imaging-guided surgery of tumor and developmental abnormalities ▸ **S. Sarnacki & I. Bloch (Télécom ParisTech)**

REFERENCE CENTERS FOR RARE DISEASES

- Pierre Robin syndrome and congenital sucking and swallowing disorders ▸ **V. Abadie**
- Developmental abnormalities and malformative syndromes in the Ile-de-France region ▸ **J. Amiel**
- Rare diseases of the skin and mucous membranes of genetic origin ▸ **C. Bodemer**
- Complex congenital heart defects ▸ **D. Bonnet**
- Constitutional bone diseases ▸ **V. Cormier-Daire**
- Rare ENT malformations ▸ **F. Denoyelle**
- Genetic deafness ▸ **S. Marlin**
- Clefts and facial malformations ▸ **A. Picard**
- Rare gynecological disorders ▸ **M. Polak**
- Rare anorectal and pelvic diseases ▸ **S. Sarnacki**
- Craniostenoses and craniofacial malformations
- Vertebral and medullary malformations

CLINICAL AND TECHNOLOGICAL BASE

CLINICAL RESOURCES OF THE HOPITAL NECKER-ENFANTS MALADES AP-HP

- 1 clinical investigation center ▸ **JM. Tréluye**r
- 1 biotherapy center ▸ **M. Cavazzana**

RESEARCH SUPPORT PLATFORM (IMAGINE)

- 1 investigation team
- 1 promotion team

17 TECHNOLOGY PLATFORMS

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

24 RESEARCH TEAMS AND 4 ASSOCIATED LABORATORIES (NECKER-ENFANTS MALADES)

L. Abel
Human genetics of infectious diseases: complex predisposition

JL. Casanova
Human genetics of infectious diseases: monogenic predisposition

A. Hovnanian
Genetic skin diseases: from physiopathological mechanisms to treatments

S. Meilhac
Morphogenesis of the heart

A. Pierani
Genetics and development of the cerebral cortex

JM. Rozet
Ophthalmological genetics

J. Amiel
S. Lyonnet
Embryology and genetics of malformations

N. Cerf-Bensussan
Intestinal immunity

E. Kabashi
Translational research on neurological diseases

M. Ménager
Inflammatory responses and transcriptomic networks in diseases

A. Rausell
Clinical bioinformatics laboratory

S. Saunier
Hereditary kidney disease laboratory

I. André
Human lymphohematopoiesis

Y. Crow
Neurogenetics and neuroinflammation

S. Latour
Lymphocyte activation and susceptibility to Epstein-Barr virus

G. Ménasché
F. Sepulveda
Molecular basis for immune homeostasis abnormalities

F. Rieux-Laucat
Immunogenetics of pediatric autoimmune diseases

M. Simons
Biology and epithelial diseases

V. Cantagrel
Genetics of neurodevelopmental disorders

O. Hermine
Cellular and molecular mechanisms of hematological disorders and therapeutic implications

L. Legeai-Mallet
V. Cormier-Daire
Molecular and physiopathological bases of osteochondrodysplasia

A. Rötig
Genetics of mitochondrial diseases

JP. de Villartay
P. Revy
Genome Dynamics and Immune System

ASSOCIATED LABORATORIES

N. Boddaert
IMAGE@*Imagine*
IRM 3 Tesla
Multimodal brain imaging

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

S. Sarnacki
IMAG2
Computational anatomy for minimally invasive imaging guided surgery of childhood tumors and developmental abnormalities

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

17 TECHNOLOGY PLATFORMS

PRE-CLINICAL

▸ Emilie Panafieu & Pierre Cherel
Animal facility
Scientific ref.: Vincent Goffin

▸ Nathalie Lefort
IPS - Organoids
Scientific ref.:
Leila Maouche-Chrétien

▸ Sylvie Fabrega
VVTG - Viral vectors
and gene transfers
Scientific ref.: Sébastien Storck

▸ Chiara Guerrera
PPN - Necker Proteomics Platform
Scientific ref.: Alain Charbit

▸ Pierre David
Transgenesis
Scientific ref.: Pierre Cherel

▸ Marcelo Simon Sola
AAV vectors

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

▸ S. Berissi
Histology
Scientific ref.: Fabiola Terzi

▸ Corinne Cordier
Cytometry
Scientific ref.: Emmanuelle Six

▸ Ivan Nemazanyy
Metabolomics
Scientific ref.: Mario Pende

▸ Sorana Ciura
Electrophysiology
Scientific ref.: Edor Kabashi

TRANSLATIONAL

▸ Christine Bôle-Feysot
Genomics
Scientific ref.: Annarita Miccio

▸ MA. Alyanakian
CRB
Scientific ref.: Corinne Antignac

▸ N. Boddaert
3T MRI
Image@*Imagine*

▸ Patrick Nitschké
Bioinformatics
Scientific ref.: Jean-Philippe Jais

▸ Nicolas Garcelon
Data Science
Clinical databases and data
warehouse

▸ M. Ménager
Transcriptomic single cell RNA

OUR GOVERNANCE

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

Imagine was awarded **University Hospital Institute (IHU)** accreditation in 2011. Thanks to this, the Institute receives an endowment allocated to it under the **Investissements d'Avenir [Investments for the Future] program,** initially until 2020, then extended until 2024 following an evaluation by a committee of international experts.

Since 2020, *Imagine* had **Institut Carnot** accreditation by the Ministry of Higher Education, Innovation and Research, accreditation that rewards the quality and dynamism of its industrial and partnership relations, and allows it to develop them.

Our founding members

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

Our governing bodies

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

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

The **IHU board** brings together laboratory directors and staff representatives to discuss the main scientific directions and how the Institute is run organizationally.

Our Social and Economic Committee (CSE)

The mission of the CSE is to ensure that employees can express their views collectively, so their interests are constantly taken into account in decisions relating to the management and economic and financial development of the company, work organization, professional training and production techniques. The CSE was set up in June 2019. In 2020, it took action and supported the leadership of the Institute and the Squad-PRA for the management of the health crisis.

OUR INTERNATIONAL SCIENTIFIC ADVISORY BOARD

Composed of eminent world-renowned scientists, the International Scientific Advisory Board issues annual recommendations to the Board of Directors and *Imagine* management regarding the Institute's scientific and strategic orientations, including the selection of new teams, the development and organization of scientific groups and the assessment of their work. In 2020, it met virtually twice, in May and November 2020.

Composition of the Scientific Advisory Board

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

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

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

Prof. Iain Drummond
Biological laboratory MDI, Bar Harbor, USA

Prof. Denis Duboule
Laboratoire de génomique du développement [Laboratory of Developmental Genomics], Lausanne, Switzerland.

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

Prof. Bernard Malissen
Centre d'Immunophénomique Marseille-Luminy, France

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

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

Prof. Antoine Triller
Institut de Biologie de l'Ecole Normale Supérieure Paris, France

The Scientific Advisory Board has welcomed a new member

Prof. Douglas Higgs joined the Scientific Advisory Board in 2020. Professor of molecular hematology and director of the MRC Weatherall Institute of Molecular Medicine at the University of Oxford, he brings expertise and a complementary perspective alongside the other 9 members. Douglas Higgs is known for his work on alpha-globin regulation and alpha-thalassemia genetics.
He is currently working to understand the mechanisms by which any mammal gene is activated and deactivated during differentiation and development.

THE EXECUTIVE COMMITTEE (G7) AND THE GENERAL SECRETARIAT

G7

Stanislas Lyonnet
Director
Embryology and genetics of malformations

Laurent Abel
Human genetics of infectious diseases: complex predisposition

Isabelle André
Human lymphohematopoiesis

Corinne Antignac
Hereditary kidney diseases

Olivier Hermine
Cellular and molecular mechanisms of hematological disorders and therapeutic implications

Frédéric Rieux-Laucat
Immunogenetics of pediatric autoimmune diseases

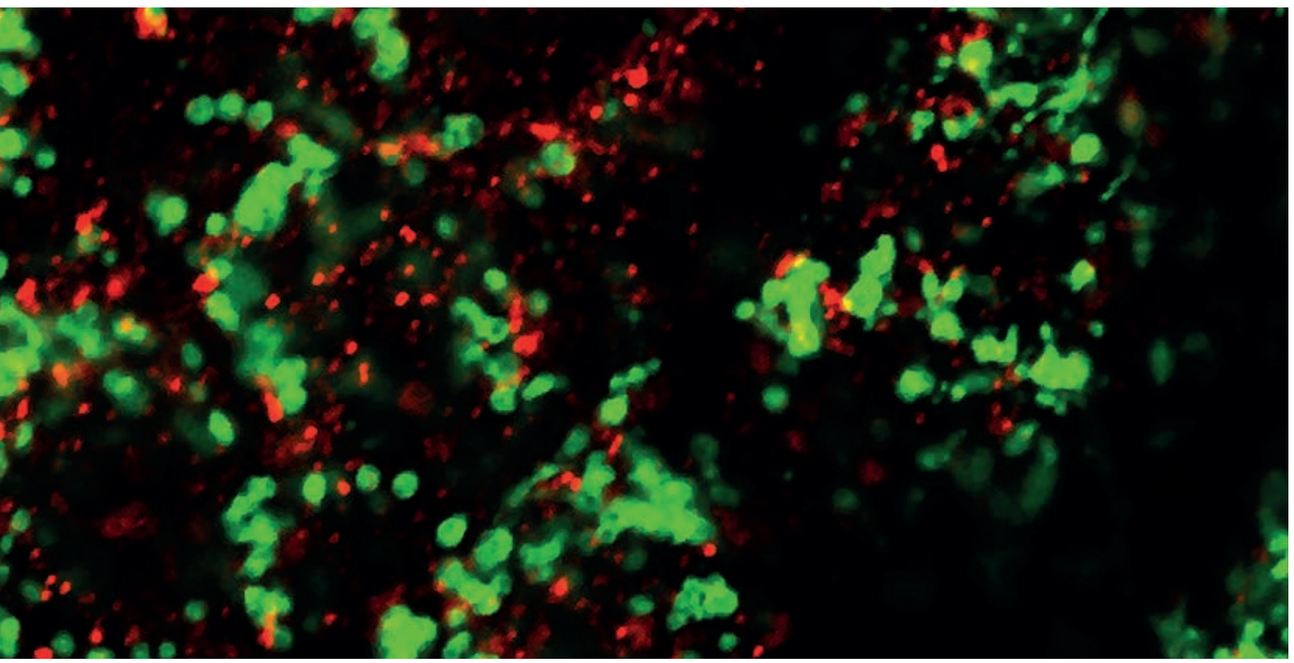
Agnès Rötig
Genetics of mitochondrial diseases

GENERAL SECRETARIAT

Laure Boquet
General Delegate

Laurent Mellier
Development and international philanthropy

Romain Marlange
Innovation and Technology Transfer



DEDICATED WORKING GROUPS (WPS)


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

WP 2: Developing genomic and bioinformatics **platforms**
Corinne Antignac


WP 3: Promoting **pathophysiological studies**
Isabelle André & Agnès Rötig

WP 4: Developing **innovative therapies**
Marina Cavazzana


WP 5: Recruiting **new talents**
Stanislas Lyonnet & Jean-Laurent Casanova

WP 6: Developing **education and training**
Frédéric Rieux-Laucat


WP 7: Social and human sciences and **societal role** of the Institute
Laure Boquet & Sandrine Marlin

WP 8: Management and **development**

WP 9: Industrial and institutional **projects**

WP 10: **Real estate** and operations

SUPPORT SERVICES

Nathalie Wuylens
Legal affairs

Romain Marlange
Innovation and Technology Transfer

Salma Kotti
Clinical research

Laurent Mellier
International development and philanthropy

Marie de Bazelaire
Communication

Séverine Delalande
Programming and finance

Emilie Resweber-Gouin
Human resources

Elodie Dandelot
Coordination of society and human and social science training programs

Anne-Marie Laurencine
Health, safety and the environment

Cécile Bureau
Internal services

Jérôme Flatot
IT

Stéphane Paillet
Operations

HUMAN RESOURCES AND LIFE OF THE INSTITUTE

An Institute spirit

In 2020, *Imagine* had nearly 1,000 people galvanized for the same cause, nearly a third of whom are students, doctoral students or post-doctoral students and 20% of whom are foreign nationals. Researchers, doctors, engineers, technicians and students are supported in their missions by the staff of the Institute's support services and teams of laboratory managers.

Imagine is committed to offering its staff a rich and varied life at the Institute, thanks in particular to its associations, the Association des Jeunes Chercheurs [Association of Young Researchers] (YR2I) and sports association (ISA), which offer professional, social and sporting activities. The Institute sets up actions to promote discussion and synergies by way of internal scientific or social events, and occasions for discussion between researchers, post-doctoral students and support services. And while 2020 did not allow as much time for fun, events and sporting activities as hoped, everything was put in place to maintain the link, even a virtual one, between the members of the Institute: discussion tools, virtual seminars, internal newsletters, live institutional debates, sport by Skype, in particular.

A corporate social responsibility (RSE) and sustainable development strategy

Since its creation, *Imagine* has placed corporate social responsibility and sustainable development at the heart of its project. With regard to its societal impact, each year *Imagine* assesses the quality of life at work, working conditions and the environment of its employees, to identify the points requiring specific actions to be implemented. Faced with the forced deployment of teleworking in 2020, *Imagine* also asked its employees what they felt about it and set up working groups to more effectively plan for the risks associated with this new way of organizing work, and to see how to develop it in the best possible way. Workshops on how to set up a home office were also offered to employees, as well as a presentation and debate on digital transformation and health at work.

In terms of gender equality, *Imagine* obtained a satisfactory score of 82 out of 100, based on the four official evaluation indicators, a score similar to that of 2019.

Everything is also being done to reduce *Imagine*'s environmental impact. In 2020, collective waste sorting points were set up on all floors of the *Imagine* building, and new coffee machines with bean grinders, generously donated by JURA and the distributor Action Café, were installed to reduce the use of capsules. *"With a view to protecting the environment and reducing our impact, a waste reduction strategy had to be set up before sorting,* notes Anne-Marie Laurencine, Health, Safety and Environment *Manager (HSE). Standardizing sorting is the first step towards a sustainable development strategy and a global waste management chain. The next step will be to develop a new waste collection and sorting circuit, to ensure that the end-to-end sorting chain is respected, and to measure our environmental impact.*" This long-term strategy will span several years and requires new resources to be put in place and habits to be changed.

SOCIAL REPORT

UMR 1163

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

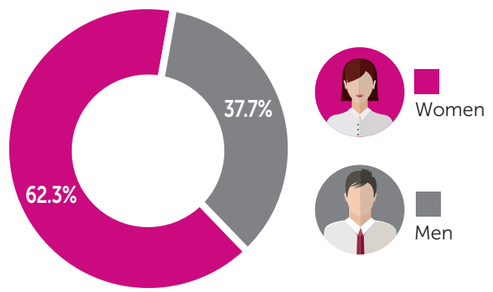
WORKFORCE

On 12/31/2020

544 PEOPLE

475.57 FULL-TIME EQUIVALENT (FTE)

Breakdown of employees by gender on 12/31/2020



AFRICA

ALGERIA: **9** - SENEGAL: **1** - MADAGASCAR: **1**
TUNISIA: **3**

AMERICA

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

ASIA

CHINA: **1** - INDE: **4** - IRAN: **1** - JAPAN: **1** - LEBANON: **3**
TURKEY: **1** - THAILAND: **1**

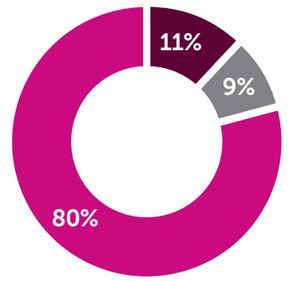
EUROPE

GERMANY: **5** - ENGLAND: **1** - AUSTRIA: **1** - BELGIUM: **2**
BULGARIA: **2** - DENMARK: **1** SPAIN: **10** - FRANCE: **436**
GREECE: **3** - REPUBLIC OF IRELAND: **2** - ITALY: **24**
LITHUANIA: **1** - LUXEMBOURG: **1** - POLAND: **2**
PORTUGAL: **3** - ROMANIA: **2** - SWITZERLAND: **1**
CZECH REPUBLIC: **1**

OCEANIA

AUSTRALIA: **1**

38
NATIONALITIES



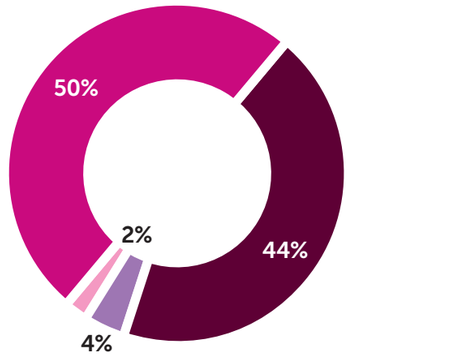
French

European Union

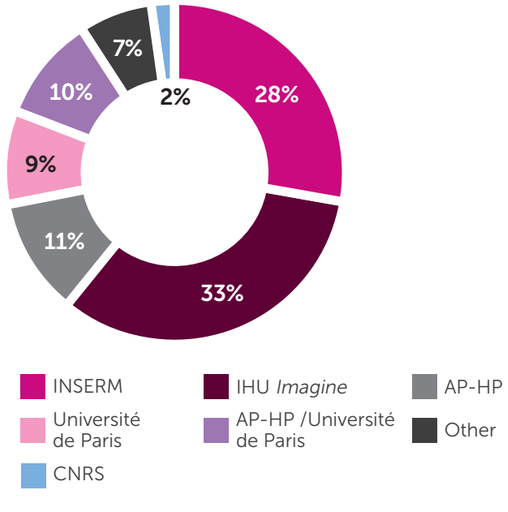
Outside the European Union

EMPLOYMENT

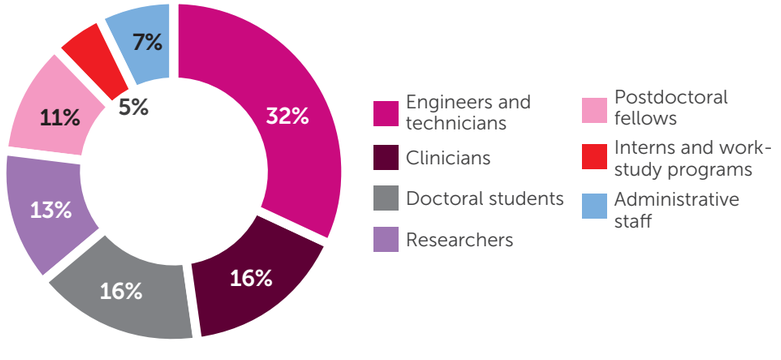
Breakdown of staff by type of contract on 12/31/2020



Breakdown of staff by employer on 12/31/2020



Breakdown of staff by occupation on 12/31/2020



Imagine Foundation

These figures only include staff employed by the *Imagine* Scientific Cooperation Foundation strictly speaking.

WORKFORCE

Workforce on 12/31/2020

159* EMPLOYEES ON 12/31/2020

153.1* FULL-TIME EQUIVALENTS (FTE) ON 12/31/2020

148.33* 148 33* AVERAGE NO. OF FTE IN 2020

14.9 EXTERNAL FTE STAFF ON 12/31/2020

162.67* EMPLOYEES ON AVERAGE IN 2020

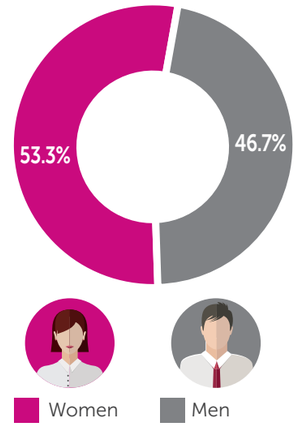
15 APPRENTICES AND INTERNS ON 12/31/2020

5 SECONDMENTS ON 12/31/2020

6 HOSTING AND VOLUNTEER WORK AGREEMENTS

* Excluding apprentices and interns

Breakdown of employees by gender on 12/31/2020



103 new contracts in 2020

73 PERMANENT AND FIXED-TERM CONTRACTS

30 INTERNSHIPS AND WORK-STUDY PROGRAMS

97 contract terminations in 2020

27 END OF WORK/STUDY CONTRACTS AND INTERNSHIPS

Employee nationalities on 12/31/2020

AFRICA

ALGERIA: **8** - SOUTH AFRICA: **1** MOROCCO: **1**
MADAGASCAR: **1** - TUNISIA: **3**

AMERICA

BOLIVIA: **1** - BRAZIL: **1** - CHILE: **1** COLOMBIA: **2**
VENEZUELA: **1** - MEXICO: **1**

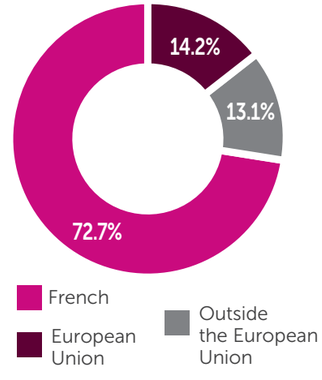
ASIA

INDIA: **1** - LEBANON: **1** - PHILIPPINES: **1**

EUROPE

ALBANIA: **1** - GERMANY: **3** - SPAIN: **5** FRANCE: **128**
GREECE: **1** - ITALY: **8** - POLAND: **1** - PORTUGAL: **2**
ROMANIA: **1** - SWITZERLAND: **1**

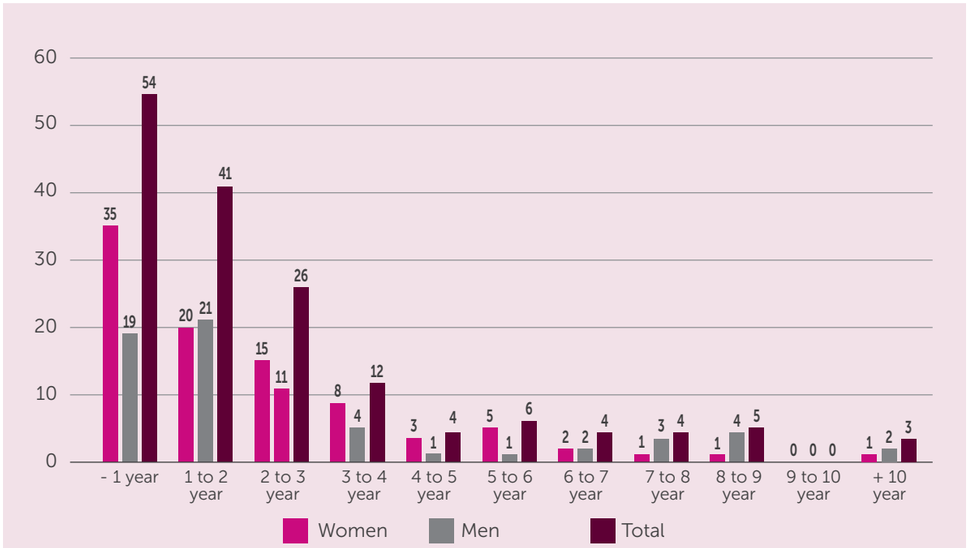
24 NATIONALITIES



AVERAGE AGE OF EMPLOYEES ON 12/31/2020

33.94 34.89 34.35

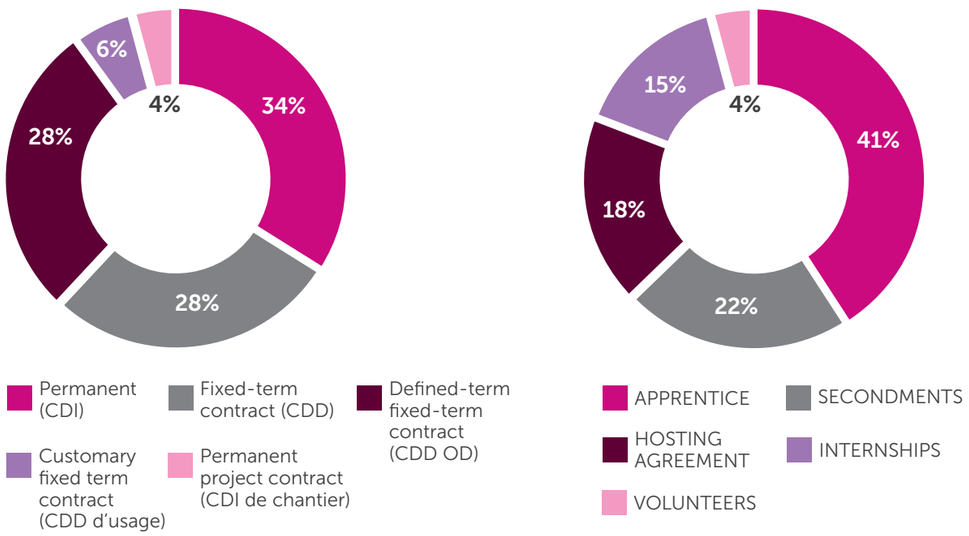
Employee length of service on 12/31/2020*



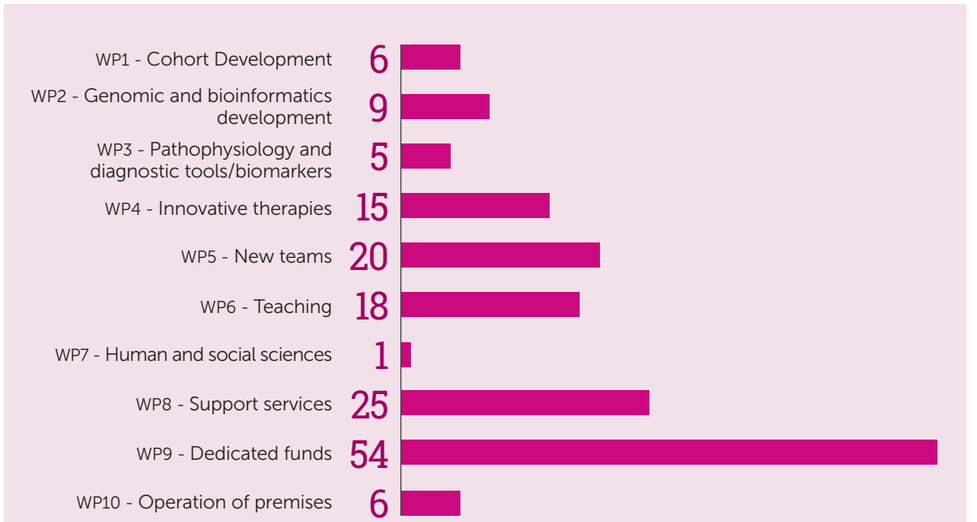
* Excluding apprentices and interns

EMPLOYMENT

Breakdown of employees by contract on 12/31/2020



Breakdown of employees by work-package (IHU program) on 12/31/2020

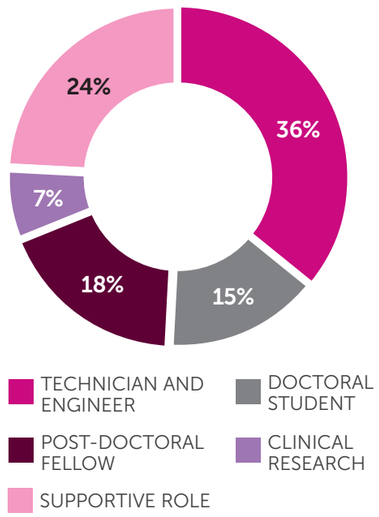


Gender equality indicator Women-Men*

82/100

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

Breakdown of employees by occupational category on 12/31/2020



INTERNS

Number of interns in 2020:

INTERNSHIPS LASTING MORE THAN ONE MONTH (FROM BACHELOR'S TO MASTER'S 2) **20** (1663 DAYS)

INTERNSHIPS OF LESS THAN ONE MONTH (FROM HIGH SCHOOL TO MASTER'S 1) **28** (198 DAYS)

THEY SUPPORT US

Although 2020 has been marked by the crisis, it has also highlighted in an extraordinary way the solidarity and generosity of companies and individuals who supported the causes that are dear to them. The presence of our donors, volunteers, patrons and friends has been all the more important this year and has greatly contributed to the determination of the teams to accelerate research on genetic diseases, in the hope of treating and relieving as many children as possible. Donations, actions of generosity or simply the existence of this support are all contributions to this fight and to this collective effort; they are very precious to us.

For all this, the Institute extends its heart-felt thanks to them.

The donations and initiatives of individuals essential for research to progress

Many patient associations and families have worked throughout the year to promote the Institute to the public and the media, pass on its discoveries, and contribute to its fight in different ways. Their work to increase our visibility, such as testimonials in the press, raising awareness in public places and sharing on social media, donation collection at events or via social networks... all of these initiatives help to give hope to children and families affected by genetic diseases.

"We support Institut Imagine *so that no other parents have to experience what we went through with Tess's disease: fear of the unknown, the future, and a lack of resources when faced with misdiagnosis. No parent is prepared for this, and every parent should be able to find answers".*

Tess's mother, Lydia B, was diagnosed after 14 months of being passed from pillar to post with OTC (ornithine transcarbamylase) deficiency, a genetic disease characterized by the abnormal accumulation of toxic compounds in the body from protein breakdown.

As for André A., it was the model of the Institute that convinced him to give to *Imagine* since its creation in 2014. *"I am sure that bringing patients, doctors and researchers together in one place saves time. It is through direct contact with children that researchers can actually see medical problems, and it is by improving this understanding that they increase the chances of finding effective solutions".*

Sponsor companies have been as generous as ever

Imagine knows that it can also count on the commitment and initiatives of sponsor companies to support its missions.

Passing on knowledge and giving access to excellent training: this is part of the Institute's fundamental and top-priority missions. Thanks to the Bettencourt Schueller Foundation, *Imagine*'s honorary patron since 2011, which strongly supports the Institute's teaching and training missions, in particular via the *Imagine* "par et à" [by and for] research program, the links between fundamental and clinical research are strengthened. The Bettencourt Schueller Foundation also provides valuable support to the Institute's conference center, which makes a major contribution to passing on knowledge through the organization of scientific conferences and seminars.

Pioneering and innovative research is one of *Imagine*'s challenges. By supporting the *Imagine* "Tailored Medicine" chair, our partner DIOR knows how decisive this ambitious work on gene therapy will be in building the medicine of tomorrow. With DIOR, we are exploring pathways to new treatments that can change the lives of thousands of children. This year, this partner with a big heart also wished to honor our nursing and hospital staff by awarding their commitment on the ground in the fight against COVID-19; and it brough the hoped-for warmth for the Christmas period at the end of difficult end-of-year circumstances.

Our new partner AXA via its Research Fund, keen to support the *Imagine* Institute and encourage the development of its research activities, wanted to engage in **the fight against cardiac and craniofacial abnormalities and malformations.** By supporting *Imagine*'s "Tête et Cœur" [Head and Heart] scientific program, AXA aims to accelerate discoveries to advance fundamental knowledge, care and technology.

Prof. Stanislas Lyonnet and Charles Robinet-Duffo, Henner Group

Loyalty is what characterizes the Henner Group that stands by our side every year with awareness-raising and fundraising actions as well as through donations. Its President and CEO, Charles Robinet-Duffo, gave a cheque for €10,000 to *Imagine* to help the institute in its fight against genetic diseases. This valuable support allows *Imagine* to increase the number of sequencing analyses. They are used to identify the genes responsible for previously unknown diseases. This is the starting point for the Institute's large-scale research projects to study the mechanisms of these diseases and pave the way for possible therapies that will help all patients affected by these diseases.

Despite a difficult economic situation, **entrepreneurs are also getting involved with *Imagine*.** Under the leadership of Eric Perrier, CEO of Viseo, the initiative by the network of Entrepreneurs Friends of *Imagine*, was launched to support an ambitious research program dedicated to learning disabilities, in order to discover their genetic origins. In its wake, other sponsor entrepreneurs are invited to join this movement to support a public health cause responding to priority issues relating to economic and social inclusion.

Imagine would like to thank Elsevier for its support and social commitment. It also thanked Banque Transatlantique's endowment fund, Derver, which enabled its teams of researchers to carry out high-impact work in the field of nephrology.

During the summer of 2020, Maison Alaïa once again joined us in an exceptional operation combining the themes of the transmission and inheritance, concepts dear to Maison Alaïa, at the heart of the Institute's research topics. Since 10 July, at the opening of its Petite Boutique, a unique and exceptional sale of pieces from old collections entrusted by friends of the Maison, has been organized for the benefit of *Imagine*.

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Talking about genetic diseases also means fighting them! Raising awareness of *Imagine* is an urgent task.

In 2020, the international magazine publishing group Condé Nast launched a new magazine dedicated to donations: GIVE, for Generosity, Innovation, Value and Emotion. It chose to generously dedicate its first issue to the *Imagine* Institute, highlighting the words and views of the management team, its researchers and families of patients, to raise public awareness of genetic disease research. This issue was sent to Vanity Fair subscribers. Its content was then reposted on the Vanity Fair website. Great publicity for the Institute!

The Havas Group continued to advise the Institute on its strategic thinking and on the deployment of its awareness campaigns, in particular.

While fundraising actions and physical operations and meetings have had to be interrupted or cancelled, we have as always been able to rely on the remote presence of our friends, who sent us their messages of support throughout the crisis and provided us with valuable help for the reopening and resumption of activity of the Institute (see page 31). We would like to thank them warmly once again.

Teddy Riner, unwavering benefactor

Sponsor of the Institute since 2012, Teddy Riner once again acted as spokesperson for *Imagine* through an awareness campaign and a call for donations to increase knowledge on genetic diseases, promoting the actions of the Institute, and calling for generosity to fight genetic diseases. Two radio spots and a national poster campaign in bus shelters, in electronic shelters and in the press were created with him. Teddy also made sure throughout the lock-down and the health crisis to send messages of encouragement to the Institute's teams to support them and ensure their continued support, a great source of joy and motivation for *Imagine*'s doctors and researchers.

The *Heroes committee* – strongly committed

On March 30, 2020, the fourth "*Heroes for Imagine*" gala was to be held, an extraordinary auction of works of art and an amazing evening. Throughout 2019 and up to the week before the event, the Heroes committee worked hard to create an event that lived up to its ambitions and those of the Institute. This auction evening was to be hosted by Gad Elmaleh, with Christie's, thanks to donations from collectors, artists, creators, gallery owners, major companies and personalities. It is with great sadness that we have had to postpone the event because of the health crisis. The committee, run since it first convened by Kamel Mennour, who was joined by Didier and Clémence Krzentowski, has continued to support us to organize the event as soon as the health conditions allow.

The last event, held in 2018, raised seven million euros to accelerate research into genetic diseases, enabling a very high-throughput DNA sequencer, NovaSeq, to be acquired. This device provides more reliable, better quality, data more quickly and at a lower cost.

THANKS TO OUR DONORS!

***Imagine* would like to extend its heartfelt thanks to its many donors.**

Whether privately, through an association, foundation or company, by giving, you have made a decision to support researchers, doctors, young patients and their families.

Whether through a donation in cash or in kind, a collection at a sporting event, a birthday or retirement party...

Thanks to you, *Imagine* is conducting the best medical research for the medicine of tomorrow, to achieve more precise and personalized treatments, so that hope can be restored to thousands of children and families".

MAJOR DONORS AND *HEROES COMMITTEE:*

- ALAÏA
- Anonymous
- Gonzague de Blignières
- Elsevier
- Groupe Galeries Lafayette
- Groupe Henner
- Marine et Bertrand Hainguerlot
- Michel Jalon
- Association KCNB1
- Galerie Kreo – Didier and Clémence Krzentowski
- La Boite Immo
- Sébastien and Armelle de Lafond
- LVMH
- Kamel Mennour
- Anne and Bruno Meniel
- Hélène de Prittwitz-Zaleski
- Phison SAS
- Jacques-Antoine Philippe and Marie Schweitzer
- Silver Autonomie
- Patrick Thomas

RESEARCH CHAIRS AND PROGRAMS:

- AXA - Research Fund
- DIOR
- Entrepreneurs, friends of d'*Imagine*
- Fondation Bettencourt Schueller
- Derver fund (Fonds de dotation Banque Transatlantique)
- MSD Avenir

SKILLS SPONSORSHIP:

- Christie's
- DGM Conseil
- Havas Group
- Marcadé Events

SPONSORSHIP IN KIND:

- Distrimedia - Action café
- Jura
- Tollens

OUR FINANCES

THIS IS THE THIRTEENTH FINANCIAL YEAR FOR *IMAGINE*.

This is the thirteenth financial year for *Imagine* Mrs. LE LOROUX, our statutory auditor, will read out her comments following my report.

After the pivotal year in 2019 when the *Imagine* Foundation's status as university hospital institute (IHU) was extended for five years by prime-ministerial decision, the 2020 financial year was aimed at accelerating the process of raising its own external, public and private resources, reflecting the progress achieved by the IHU and the ambitions of its 2019-2028 strategic roadmap.

The **unprecedented health and economic crisis** in 2020 has had a very strong impact on this dynamic, requiring the Foundation to manage the crisis, whose repercussions it presented to the Board of Directors at its meetings during 2020. This crisis management was combined with **tight steering** of all the measures in its roadmap as well as a **response** aimed at immediately investing in research projects related to COVID-19, rethinking the fundraising models and maintaining a sufficient pace of development – despite the constraints – to guarantee the **solidity of the institute at the end of the crisis**.

The negative impacts of the health and economic crisis are both due to the **suspension of major revenue sources from public donations** and the **necessary postponements of events:**

- Postponement of the ***Heroes*** **charity gala;**
- Slowdown in the fulfilment of commitments by **major donors;**
- Delay in negotiations underway on **industrial contracts,** with a rebound effect on 2021 (49 industrial partnerships contractualized at the end of 2020);
- Slowdown in the implementation of **earmarked financing acquired;**
- Decisions to **postpone a certain number of actions and related expenses in 2021** (in particular *Imagine* calls for tenders, the 2nd Crosslab event, accelerator Springboard, Innogrant Bioentrepreneurs, Human and social sciences and rare diseases, studies concerning spaces at *Imagine*, direct marketing).
- **Additional costs** relating to the implementation of precautionary health measures (equipment and protocols) and support for young researchers (extension of contracts);
- **Natural postponements of recruitment and delays in the implementation of projects** (in particular slowdown in the execution of projects launched for the *Imagine* call for tenders as well as the suspension of the concrete forms of the major strategic partnerships initiated in 2019 with Pasteur and EPFL).

The financial year was steered with caution so as not to place too much strain on the implementation dynamic of the IHU roadmap by safeguarding the strategic priorities established during its validation: priority was given to scientific resources calling in particular for the maintenance of the IHU core program, the launch of the "new team" international call for tenders and the continuation of the Springboard program, which depends on additional Go/No Go phases so the risk can be managed.

This management was carried out while the **Institute was in a position of financial strength**, reflected both in its own funds (initial funding of €12.9 million fully reconstituted by the surpluses of previous budgetary years, retained earnings set at €3 million at the end of 2019) and its cash position (€20.9 million at 30/12/20 excluding capital invested in life insurance for €3.7 million). This financial strength has been backed up by the extension of IHU accreditation, resulting in an exceptional payment in 2020 of €10.4 million for the payments agreed on with the ANR.

The board validated this strategy by calling to make the most of this dynamic of solidarity that the results of the Institute's research teams working on COVID 19 was bound to produce, from both its founders, who expressed their renewed support for the Institute, and its donors, whose loyalty stood fast during the crisis.

The same board asked the Institute not to slacken the pace, while planning and exercising caution.

Ultimately, the 2020 financial year reflects a **moderate slowdown in the activity development dynamic** of the Institute given the **sustained pace experienced by the continuation of major cross-cutting programs:** DIM gene therapy, RHU3 for ciliopathies, RHU4 for primary immune deficiencies. 2020 was marked by significant successes in this area: strengthening of the RHU3 C'IL LICO whose industrial partner, the start-up MEDETIA, successfully raised funds right in the middle of the lockdown, ensuring the sustainability of the project; consolidation of the RHU 4 ATRACTion by signing its consortium agreement with all academic and industrial partners with the receipt of the first advance payment.

Despite the lock-down, the operations that had to be done to launch the **single-cell analysis platform**, financed by the Ile de France region and BPI France, have been completed. Obtaining **INSTITUT CARNOT** accreditation also acknowledges the value of the partnership dynamic with the socio-economic world. Finally, the crisis did not prevent the **major donors** from working alongside the institute, both by pursuing a very strong fundraising mechanism – even if lower than the target initially put in the 2020 provisional budget – and by setting up the campaign committee to launch a very solid dynamic for the 2021 financial year and beyond.

All these balances result in a **1% increase in the budget, on the face of it**, in the income statement, which must be corrected for accounting adjustments applied to dedicated funds due to the new regulations. So, **operating expenses alone increased by 15% in 2020, due totally to the increase in implementation expenses for financing earmarked for public and private hosted contracts,** caused by repayments to the partners of the DIM and RHU consortium. This growth is well below the initial target but still considerable, and just slightly lower than that of the previous year.

The 2020 financial year was also marked by the **reorganization of the administrative and financial department** with the recruitment of a Programming and Finance Director, after a long vacancy in the previous position of finance manager, the use of an accounting firm for the reorganization of the department and the retreatment of accounts and the launch of the recruitment of a management controller, which had been planned for several years.

Finally, the 2020 financial year was affected by the **changes in accounting methods resulting from the new accounting regulation,** applicable as of 1 January 2020, producing significant impacts, in particular on the reclassification of investment subsidies, the recording of agreements based on their multi-year amount and the transformation of resources not consumed into dedicated funds or accrued income.

These processing changes had the effect of increasing the 2020 result, which was consequently significantly higher than expected, closing with a **€3 million surplus.** At the same time, the retained earnings at the end of 2020 were deducted from investment grants of €2.8 million previously included in the income statement and then switched to the equity in the liabilities section of the balance sheet (neutral impact on total equity). A suggestion was, therefore, made to the Board of Directors to allocate the entire 2020 surplus to retained earnings to replenish the liquid reserves up to the amount initially provided for in this account, namely **retained earnings brought forward to €3.1 million after allocation of the 2020 result.**

These results demonstrate that the management of the measures as set out to the Board of Directors in 2020 enabled a deficit to be avoided with regard to current activities in 2020 despite the crisis, thereby **keeping all the reserves constituted** in respect of i) the retained earning account ii) the PIA-IHU 2020-2024 subsidy, both in deferred income and past investment subsidies, and iii) the initial funding.

The balance sheet

It should be noted, the balance sheet is a summary statement that makes it possible to describe in terms of jobs and resources the financial position of *Imagine* on the closing date of the accounts, i.e., Thursday, December 31, 2020.

At that date, it stood at **€84,278,228** compared with **€35,821,909** in 2019. This increase in face value is linked to the inclusion in the balance sheet of multi-year contractual amounts in respect of public and private subsidies within deferred income, which therefore amounted to **€53,652,511** compared with **€2,769,637** in the 2019 balance sheet, which only included deferred income on industrial contracts for the tranches duly invoiced.

Net assets	12/31/2020	12/31/2019	%
Fixed assets	€ 10,449,697	€ 7,338,006	42%
Current assets	€ 73,828,531	€ 28,483,903	159%
Total	**€ 84,278,828**	**€ 35,821,909**	**135%**

Net liability	12/31/2020	12/31/2019	%
Associative funds	€ 20,145,281	€ 18,750,101	7%
Provision for liabilities and expenditure	€ 1,047,196	€ 992,290	6%
Dedicated funds	€ 2,368,660	€ 6,848,652	-65%
Debts	€ 60,717,091	€ 9,230,867	558%
Total	**€ 84,717,091**	**€ 35,821,909**	**135%**

The gross amount of fixed assets at the end of 2020 was €26.9 million (compared with €21.5 million in 2019), including €17.6 million in laboratory equipment.

The value of fixed assets increased in 2020 due to the integration into financial fixed assets of the life insurance policy held by the Foundation for €3.7 million and non-financial fixed assets for the financial year.

Intangible and tangible fixed assets

The net value of tangible fixed assets (€6.5 million) and intangible assets (€36,000) decreased due to an amount of depreciation greater than the acquisitions for the year.

Intangible and tangible assets amounted to €2.06 million. The main acquisitions were for additional bioinformatics storage servers, the replacement of IT infrastructure servers, the acquisition of innovative technologies for new single cell analysis and electrophysiology platforms, the co-financing – under the heading of DIM gene therapy – of multi-team technological equipment for the detection of biomarkers and the transformation protocols related to genome editing as well as the acquisition of various pieces of laboratory equipment for the start-up, Medetia, located on site, the new website of the institute and the acquisition of racks for the SFR animal facility platform as part of the installation of the Faculté Necker branch.

The main works involved various building maintenance operations and maintenance of its infrastructures

Financial fixed assets

In 2020, Step Pharma, in which *Imagine* holds shares, is still yet to generate revenue at its stage of development and is pursuing an active research and development policy to which it allocates all its funding. In view of the fundraising round in March 2021 for €35 million and the nominal value of the shares acquired in this respect, it was decided not to apply any depreciation on top of that recorded for previous years (i.e., €358k of depreciation for previous years out of a total amount held of €506k).

Other financial assets comprise the life insurance investment held by the Foundation (€3.7 million) and the securities held within the Smart Immune start-up (€71,000).

Receivables

Receivables from customer accounts totaled €6.14 million, an increase of €2.7 million, mainly related to invoices to be issued to the founding members for their contributions to the building as well as receivables from invoices from APHP-Necker for the reimbursement of operating costs for the hospital portion of the building over the last three financial years, the adjustment of which is under way. None of these receivables is considered risky.

Other receivables were valued at €46.48 million in 2020. They consist mainly of accrued income on all multi-year public and private agreements currently being executed in respect of contractual income and remaining to be paid over future years. Public grants to be received amounted to €40.5 million, including €16.5 million for the PIA-IHU grant, €12.3 million for the RHU3 and 4, €6.7 million for the Gene Therapy DIM, €2.6 million for the generic ANR calls for projects won by the *Imagine* teams and €1.5 million in European funds. Private contributions to be received amount to €2.7 million (Devodecode project for MSD Avenir funding in particular).

Equity capital

The Foundation's equity consists of its initial endowment, fully reconstituted to the amount of €12.9 million at the end of the 2017 financial statements, retained earnings from previous financial years, amounting to €86.5 million, income for 2020 (+€3.017 million) and investment grants received by the Foundation (net value of €4.14 million).

So, equity totaled €20.145 million and the PIA financing for equipment in previous years was allocated as an investment subsidy in application of the new accounting regulation. This accounting causes switching between i) retained earnings ii) profit for the year and iii) investment subsidies.

Capital increased significantly in 2020 (+€1.4 million) due to the exceptional operating surplus in 2020 linked to the accounting retreatments carried out to adjust the revenues earmarked according to the rate of progress of the projects for the dedicated funds (Carnot, DIOR and processing of operating and resourcing costs for hosted contracts) and subsidies to be received from the gene therapy DIM.

Dedicated funds

In accordance with the new accounting regulation 2018-06, dedicated funds are the liability section which records, at the end of the financial year, the part of the resources allocated by third-party funders to defined projects, the execution of which is in progress, in accordance with the commitment made to them, and of which the unused balance not consumed must be confirmed in the accounts.

They amounted to €2.36 million at the end of 2020 compared with €6.85 million in 2019, their decrease being linked to the change in accounting method made in 2020 by switching to deferred income from public and private operating subsidies, previously managed as dedicated funds (€6.09 million, of which more than half for the PIA-IHU subsidy). Conversely, from 2020 they include private investment subsidies, previously treated as equity (€0.7 million). The neutralization of these effects makes it possible to consider the increase to be €0.9 million, reflecting both the slowdown in the pace of recovery of funding earmarked due to the crisis and the obtaining of new donations and sponsorships earmarked by the Institute's teams.

Debts

Debt amounted to €60.71m compared with €9.23m in 2019. This increase is linked to the restatement of multi-year public and private grants in deferred income for €53.7 million, including €20.8 million for the PIA-IHU grant and €14.4 million for the RHU3 and 4 grants. Tax and social contribution liabilities increased significantly (€2.26 million at the end of the year) due to a provisional entry linked to a VAT refund on the CPER government subsidy made in favor of the acquisition of animal facility equipment for the Université de Paris as an entity hosting the Necker federating structure; this €422,000 transaction will be settled in 2021 when the assets concerned are transferred. Other liabilities comprise assets to be paid. The deferred income on industrial contracts increased slightly in 2020, from €2.77m in 2019 to €2.95m in 2020.

Income statement

For the record, the 2020 income statement covers all the flows that positively or negatively alter the financial situation of *Imagine* in 2020, tracing the products that generate wealth and the expenses that reduce it and enable to the Institute to operate.

The income statement of *Imagine* is as follows:

- **Revenue: €27,011,907** (compared with **€26,692,829 in 2019,** 22,984,543 in 2018, 18,349,515 in 2017, 16,801,238 in 2016 and 19,155,981 in 2015),
- **Expenditure: €23,995,112** (compared with **€26,570,383 in 2019**, 22,014,465 in 2018, 16,959,388 in 2017, 14,841,491 in 2016 and 14,373,478 in 2015).

The surplus is **€3,016,794** in 2020 compared with €122k in 2019 and €970k in 2018.

	12/31/2020	12/31/2019	%	Change
TOTAL REVENUE	€ 27,011,907	€ 26,692,829	1 %	€ 319,078
TOTAL EXPENSES	€ 23,995,112	€ 26,570,383	-10 %	- €2,575,271
RESULT	**€ 3,016,795**	**€ 122,446**	**2364 %**	**€ 2,894,349**

2020 Revenue

Imagine's revenue was stable in 2020: from €10 million in 2014 to €16.8 million in 2016, then €18.3 million in 2017. They reached €22.98 million in 2018, €26.69 million in 2019 and came to **€27.01 million in 2020.**

The stability of operating income can be attributed to:

- A very significant increase in public subsidies both for the PIA-IHU (payments of €10.441 million in PIA subsidies in 2020) and other public subsidies (payments of €8.749 million in 2020),
- On the face of it, the reduction in increase of the switch to deferred income of related funds not consumed in respect of sums already paid (i.e., €4.5 million for the PIA-IHU and €5.6 million for other public subsidies)
- A slight decrease in the recovery of dedicated funds from €8.9 million to €6.92 million
- A sudden significant increase in the invoicing of industrial contracts, partially offset by the recovery of the deferred income constituted at the outset
- A continuation of donations and patronage, admittedly below the forecast, but whose very high level demonstrates the fundraising dynamic with major donors and foundations, initiated by the Foundation.

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

Operating income amounted to €9 million in 2014, €14.8 million in 2015, €18.9 million in 2018 and €17.04 million in 2019; it amounted to **€25.35 million** in 2020 despite the health crisis and the postponement of the Heroes charity evening.

On the face of it, the increase in operating income is due to the application of the new accounting regulations, which include dedicated funds that previously appeared at the bottom of the income statement. After offsetting the €6.92 million in use of dedicated funds in 2020 (compared with €8.92 million in 2019), retreated operating income totaled **€18,434,008, up 8% compared with 2019**.

This **increase is that in public funding and operating subsidies,** which amounted to €11 million in 2020 and €9.3 million in 2019, even though new accounting treatments are detrimental to this revenue item in 2020 because of private grants being switched to financial contributions (equivalent to €856 thousand in 2019) and funds not used during the year being removed and then included in deferred income (representing €4.8 million in 2019).

Services sold correspond to **industrial contracts** (€1.5 million), industrial hosting fees (€0.35 million) and platform services (€0.46 million). **The crisis halted their uninterrupted growth** over the last five years, from €1.2m in 2015 to €2.46m in 2017 and then €2.93m in 2019. They came to €2.3 million in 2020. Although invoicing for the year is lower than expected, the dynamic of industrial partnerships (€1.1m in 2016, €1.7m in 2017, €1.9m in 2018, €2m in 2019 and €0.99m in 2020) was not compromised with regard to deferred income to be claimed in 2020 for €2.9m and the rebound effect on 2021 of postponed negotiations).

Donations were **down significantly** compared with previous years, at €2.1m below the levels of 2019 (€3.32m) or 2017 (€3.34m). Their decrease should nevertheless be put into perspective due to the new allocation in financial contributions of funding from associations, foundations and endowment funds (€1,671k in total). This concerns in particular the funding of the training program by the Bettencourt-Schueller Foundation to the sum of €478k recorded as donations allocated in 2019 and shown excluding resources related to public donations in 2020 to the sum of €295k or the donation of an endowment fund shown as non-earmarked manual donations to the sum of €300k in 2019 and in financial contributions for €400k in 2020.

On a like-for-like basis, resources linked to donations, sponsorships and financial contributions from non-profit organizations have been maintained due to the increase in donations from private individuals (major donor campaign effect and direct marketing), the execution of the Dior chair for personalized medicine (worth 2 annual tranches over the same financial year) offsetting the decrease in resources paid by foundations and associations in this transition year after the closing of prior agreements between EDF and Bettencourt Foundation.

This level was maintained because of the last invoices being made out at the beginning of the 2019 financial year for the 2018 Heroes gala. The 4th gala could not, however, be held in 2020 due to the health crisis.

Financial contributions in 2020 will be grouped together with contractualized funding from foundations and associations previously recorded as donations or subsidies to the sum of €1.7 million. Once retreated on a like-for-like basis, they were up by €265k thanks to private grants.

Financial income fell slightly in 2020 against a backdrop of general gloom in the money markets (€24,000 in 2020 compared with €33,000 in 2019; €73,000 in 2018; €91,000 in 2017; €45,000 in 2016; €51,000 in 2015 and €71,000 in 2014). The healthy situation of the Institute's treasury, and its liquidity, gives it the necessary agility to maintain the pace of project development. The institute conducted an in-depth investigation at the end of 2020 to establish an infra-annual piloting plan, the only way of identifying any potential for additional placements.

Exceptional income of €1.622 million in 2020 compared with €696,000 in 2019, corresponds to the share of investment grants previously recorded as liabilities on the balance sheet; this change was made because of the restatement of €1.1 million in PIA grant shares and other public grants which, with the exception of investment grants from the Gene Therapy DIM, were previously treated as dedicated funds.

2020 expenses

The Foundation's expenses decreased by 10% in 2020, to €23.99 million compared with **€26.57** million in 2019; €16.6 million in 2017; €14.8 million in 2016; and €14.4 million in 2015. They break down into operating expenses, financial expenses and extraordinary expenses.

Their rate of change in 2020 was reduced by the reprocessing of dedicated funds for grants and financial contributions.

The neutralization of these shows a 12% increase in current expenditure in 2020.

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

This change is to be corrected for carryforwards in dedicated funds that were not previously included (€1.7 million in 2020).

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

This dynamic resulted directly in an €0.632 million increase in personnel expenses between 2019 and 2020 (+7% on average, +28% on hosted contracts, strong growth in other platforms, particularly in connection with the inauguration of the Single Cell platform).

Other expenses (services and consumables) fell by 2%, even though expenses on hosted contracts for subsidies and industrial contracts increased significantly. However, payments to partners of the RHU and DIM consortia increased very significantly for the second year (€2.6 million in 2020 compared with €1.3 million in 2019).

Depreciation is still stable in 2020 (€2.2 million) as in 2019.

Financial and exceptional expenses represent accounting transactions and varied between 2019 and 2020 by €134k due to the correction being applied in 2018 to fixed assets.

The **result** for the financial year shows a surplus of €3.017 million, and must be analyzed with regard to the accounting retreatments carried out on the 2020 balance sheet in connection with the implementation of NPC 2018-06, relating to i) the exceptional recovery of the share of investment subsidy under the PIA for €1.05 million ii) all the retreatments made on the earmarked financing managed as dedicated funds or deferred income to align the statement of the receipt as the project progressed, revealing in 2020 exceptional revenue for recovery of previous funds or the recording of grants receivable, to the sum of €2 million.

Annual statement of the use of resources

For the first year, we are offering you an income statement by origin and purpose (CROD) and for the eighth consecutive year, we are offering you an annual statement of the use of resources (CER) with allocation of resources collected from the public by type of use, so *Imagine* donors and patrons can trace the contribution of donations to the scientific project. These new accounting treatments are detailed in the notes to the financial statements.

- CROD

Total funds break down to 88% on social missions, 4% on fundraising costs and 8% on all operating costs.

Presentation of resources

· **Resources collected from the public,** coming to a total of **€2,063,118** (versus **€3,317,803** in 2019), consist of three lines:

- Manual donations, coming to a total of **1,413,118** euros,
- Sponsorship, coming to the sum of **650,000** euros (Dior sponsorship for 2019 and 2020). These amounts between over the two years cannot be compared since the NRC has allowed funds from associations, foundations and endowment funds to be classified as financial contributions.

· **Revenue not related to GP come under three headings:**

- **Subsidies and other public subsidies** consist in particular of IHU funds and other public ANR and Ile de France region subsidies amounting to **€12,547,918;**
- **Financial contributions** coming to a total of **€1,671,286**; this category was not previously present in *Imagine*'s accounts. It now includes all funds from associations, endowment funds and foundations,
- **Other revenue not related to public donations** coming to the sum of **€3,809,392.**

The total resources for the financial year recorded in the income statement is therefore **€20,091,714** plus the sum carried forward for unused allocated resources over previous financial years **€6,920,193** i.e., a total of **€27,011,907** (versus €26,692,829 in 2019).

Presentation of employment

Employment costs come to a total of **23,995,1123**, with the CROD reporting the surplus generated in the current financial year and two-thirds of which is linked to the favorable impact of accounting restatements imposed by NRC 2018-06 and the harmonization of the treatment of operating subsidies, investment subsidies and financial contributions. Part of this impact can be correlated with the CER. 88% of employment expenditure is on social missions (including the constitution of dedicated funds) versus 87% in 2019, 4% on fundraising costs, which are broken down into two blocks (GP-related fundraising costs amounting to 3% and other funds (less than 1%) and 8% for all operating costs.

a. Social missions €19,401,403

b. Constitution of dedicated funds for social missions €1,724,294
> This makes a total of 21,125,698 (88%) for all social missions allocated over the year and in the future

c. Costs of appealing for public donations and seeking other funds €892,327 (4%)

d. Operating expenses € 1,922,180 (8%)

- The CER

The CER no longer lists financial contributions from previously listed private non-profit organizations as public donation resources. 92% of total employment is dedicated to social missions (including the creation of dedicated funds), 3% for fundraising costs and 3% for all operating costs, the balance corresponding to the surplus generated exceptionally in 2020 (€338k linked to the implementation of the NRC corresponding to expenses recorded over previous years through the recovery of dedicated funds).

Donations collected in 2020 amounted to €2,063,118 and were supplemented by a change in dedicated funds of €799,308, corresponding to the recovery of donations collected over the years. Consequently, the resources collected from the public and used in 2020 total €2,523,998 and are broken down as follows:

e. Social missions €1,505,694 (60%)

f. Constitution of dedicated funds for social missions €851,004 (32%)
> a total of (92%) for all social missions allocated over the year and in the future

g. Costs of appealing for public donations € 83,650 (3%)

h. Operating expenses € 83,650 (3%)

> The call for donations and operating costs are calculated on the basis of the social missions allocated over the year and not for the dedicated funds.

Mrs. Isabelle LE LOROUX, our Statutory Auditor, will read out her reports. The 2020 accounts will then be submitted for your approval.

Caroline Young, Treasurer

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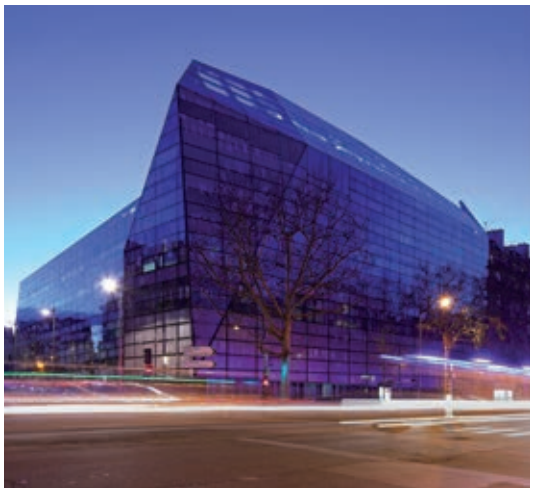

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