Research evaluation

EVALUATION REPORT OF THE UNIT

IHU Imagine - Institut des maladies génétiques

UNDER THE SUPERVISION OF THE FOLLOWING ESTABLISHMENTS AND ORGANISMS:

Université Paris Cité - UP Cité,
Institut national de la santé et de la recherche médicale - Inserm

EVALUATION CAMPAIGN 2023-2024
GROUP D

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High Council for evaluation of research and highter education

In the name of the expert committee :

Susan Chan, Chairwoman of the committee

For the Hcéres :

Stéphane Le Bouler, acting president

Pursuant to articles R. 114-15 and R. 114-10 of the Research Code, the evaluation reports drawn up by the expert committees are signed by the chairmen of these committees and countersigned by the President of Hcéres.

To make the document easier to read, the names used in this report to designate functions, professions or responsibilities (expert, researcher, teacher-researcher, professor, lecturer, engineer, technician, director, doctoral student, etc.) are used in a generic sense and have a neutral value.

This report is the result of the unit's evaluation by the expert committee, the composition of which is specified below. The appreciations it contains are the expression of the independent and collegial deliberation of this committee. The numbers in this report are the certified exact data extracted from the deposited files by the supervising body on behalf of the unit.

MEMBERS OF THE EXPERT COMMITTEE

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	Ms Hélène Puccio, Institut Neuromyogène - PGNM
Experts:	Mr Alain Buisson, Communauté Université Grenoble Alpes
	Ms Bénédicte Durand, Université Claude Bernard Lyon 1 - UCBL
	Mr Douglas Higgs, University of Oxford, United Kingdom
	Mr Philippe Huber, CEA - Commissariat à l'énergie atomique et aux énergies alternatives, Grenoble
	Mr Gaetan Lesca, Université Claude Bernard Lyon 1 - UCBL (representative of CNU)
	Mr Antonin Morillon CNRS, Paris
	Ms Janine Reichenbach, University of Zurich, Switzerland
	Mr Alexandre Reymond, University of Lausanne, Swizerland
	Mr Jean-Jacques Schott, Inserm, Nantes (representative of CSS Inserm)
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Mr Philippe Ruszniewski, Université Paris Cité

CHARACTERISATION OF THE UNIT

- Name: Institute of Genetic Diseases - IHU Imagine
- Acronym: IMAGINE
- Label and number: UMR1163
- Number of teams: 24
- Composition of the executive team: Head of the unit for 2019 - 2025: Prof Stanislas Lyonnet; Head of the unit for 2025 – 2023: Prof Bana Jabri

SCIENTIFIC PANELS OF THE UNIT

SVE Sciences du vivant et environnement
SVE3 Molécules du vivant, biologie intégrative (des gènes et génomes aux systèmes), biologie cellulaire et du développement pour la science animale

THEMES OF THE UNIT

IHU Imagine studies rare genetic diseases, with a vision of integrating basic research with clinical practice. Its core missions comprise patient-focused research, innovative care, education and training, and technology transfer.

HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

IHU Imagine belongs to three supervising bodies: the Public Hospitals Group of Paris (AP-HP), Inserm and Université Paris Cité. It is also financially supported by the city of Paris, the French Muscular Dystrophy Association (AFM-Téléthon) and the Fondation des Hôpitaux de Paris. Imagine was established in 2007 and given University Hospital Institute (IHU) status in 2011. The current 19,000 m2 building was opened in 2013 on the Necker Hospital campus to house scientific teams, core facilities and an outpatient clinic (APHP). Imagine was founded by Alain Fischer, Claude Griscelli and Arnold Munich, and directed by A. Fischer until 2016. Stanislas Lyonnet is the current unit director (2016-2024). The next Director will be Bana Jabri, who was selected through an international call. She will begin her 5-year team in January 2025.

RESEARCH ENVIRONMENT OF THE UNIT

Imagine is composed of 1/the mixed research unit UMR1163, directed by S. Lyonnet, which comprises nineteen teams (18 plus 1 ATIP-Avenir), 2/the Imagine Foundation for Scientific Cooperation (FCS), also directed by S. Lyonnet, which represents the private financial arm that manages both the public grants and private funds, 3/ 5 IHU research teams that are functionally attached to the FCS, and selected to complement the Imagine themes by the Executive committee and scientific board (SAB). Four of the five IHU teams will join UMR1163 in the next contract. Four adjunct teams from the broader Necker Hospital campus, with complementary interests and expertise, are also associated with Imagine, but they are not evaluated here. Additionally Imagine has close relations with the Necker-Enfants Malades hospital (8 clinical units, 31 reference and two clinical investigation centres). These relations have allowed >45,000 patients to be consulted per year on the Necker campus. Other research and service units on the campus provide technical platforms that can be used by the institute teams.

The unit governance is ensured by the Executive committee (G10), and supported by the general secretariat, the technology transfer office (TTO), and the IHU council. Together, they are advised by the SAB and the Board of Trustees of the Foundation.

The G10 is made up of the unit director, and team leaders from each of the work packages of the Imagine program (cohorts; genomics and bioinformatics; pathophysiology; clinical research; scientific sourcing; training and education; health, science and societal role; management-organisation-development; hosted contracts; real estate). The G10 meets twice a month to discuss strategies and practical issues.

The TTO plays a prominent and elevated role in the governance, which highlights the unit's desire to bring its research rapidly to the patient. The TTO committee makes strategic decisions on the valorisation of scientific results and interactions with economic and industrial partners. It is chaired by the unit director at monthly meetings to optimize available resources. The unit obtained the Institut Carnot label in 2020, in recognition of the quality of its relations with pharma and the socio-economic sphere.

The IHU council (team leaders, theme leaders, representatives of the technical staff, students/postdocs and researchers) meets four times a year and is associated with core facility development, the unit roadmap, and election of the new director.

The SAB is composed of ten-twelve internationally recognised scientists that represent the scientific interests of the unit, and provide advice on strategy, budget allocations, and the selection of new research groups. It meets one to two times a year.

The Board of Trustees is composed of representatives from the founding members (AP-HP, Inserm, Université Paris Cité, AFM-Téléthon, Fondation des Hôpitaux de Paris, Paris city council), elected representatives of researchers and teacher-researchers, private sector personalities. They meet two to three times a year to validate strategic decisions and financial affairs.

The unit roadmap is defined every ten years (currently 2018-2028) and validated by the different bodies. Its objectives are to: accelerate patient diagnoses; increase research into disease mechanisms; increase clinical trials; find common means to treat various diseases; enrich patient cohorts; recruit external teams; invest in new technology, bioinformatics and genomics; support young scientists; create a centre to model diseases. The financial roadmap defines the unit's ambitions to increase its resources from 61 M in 2018 to 82 M euros in 2025. In 2021, the resources were 63 M euros.

The unit hosts numerous forums including: group leader seminars, IHU club, technology transfer meetings, seminars for invited internal and external scientists, full-day themed seminars, young researcher association seminars, ICaRP meetings, Café des Chercheurs.

The unit is supported by administrative services that include but is not limited to: clinical research, communication, fundraising, business development and technology transfer.

Seventeen platforms and services form the backbone of the unit. They include: proteomics, FACS, DNA biobank, single-cell analysis, iPSCs, bioinformatics, transgenesis, gene transfer and recombinant adeno-associated viral (rAAV) vectors, genomics, imaging, IRM3T, data science, pre-clinical model facilities, histology, electrophysiology, neurobehaviour.

UNIT WORKFORCE: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	45
Maîtres de conférences et assimilés	25
Directeurs de recherche et assimilés	25
Chargés de recherche et assimilés	44
Personnels d'appui à la recherche	129
Sous-total personnels permanents en activité	**268**
Enseignants-chercheurs et chercheurs non permanents et assimilés	73
Personnels d'appui non permanents	101
Post-doctorants	46
Doctorants	98
Sous-total personnels non permanents en activité	**318**
Total personnels	**586**

DISTRIBUTION OF THE UNIT'S PERMANENTS BY EMPLOYER: in physical persons at 31/12/2022. Non-tutorship employers are grouped under the heading "others".

Nom de l'employeur	EC	C	PAR
Inserm	0	56	38
AUTRES	13	11	36
UNIVERSITÉ PARIS-CITÉ	39	0	10
Total personnels	**52**	**67**	**84**

GLOBAL ASSESSMENT

The unit's scientific objectives are: to identify rare genetic diseases, understand, treat, valorise and train, were achieved with the identification of novel genetic disorders linked to a variety of diseases and the characterisation of disease mechanisms. The unit showed an impressive capacity to bring its findings to the clinic.
The unit's finances were outstanding. The unit benefited from Programme d'Investissements d'Avenir (PIA) money (17 M €), philanthropy and grants from public and charity sources, equal to 63 M euros in 2021.
Human resources and gender parity were excellent.
The attractiveness of the unit was outstanding. The unit recruited five new team leaders in the past contract, 11 scientists with permanent positions (either Inserm or dual university/hospital positions), and was successful in recruiting at the international level its future director. The unit had excellent performance in training PhD students (111 PhD students).
Scientific production was outstanding. The unit published >5000 papers, with 730 in journals with excellent visibility and >330 in journals with the highest visibility (Nature, Lancet, Science, Cell, New Engl J Med, JAMA). The unit is a leader in the rare disease community. The scientific results have a lasting impact on patient care.
The contribution of research activities to society of the unit was outstanding, with the Carnot Institute label in 2020 to develop research partnership with the pharma sector and the socio-economic sphere. The unit had eight industrial transfers of patents during the reporting period giving rise to eight start-ups. The unit has a dedicated work package to contribute to sharing its knowledge with the general public.

DETAILED EVALUATION OF THE UNIT

A - CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

"A balance needs to be maintained to ensure that the focus on patients and unravelling the defects in individuals with rare diseases and cohorts of patients is maintained and not lost through pressure to bring in groups with strong "basic" science methods."
- Imagine has maintained a strong link with the clinic. It increased its links to rare disease reference centres (CRMRs) from twelve in 2017 to 31 in 2022; 45K patients are included in these CRMRs.

"The Unit should consider expanding links to groups working in resource poor regions."
- This was achieved. Strong collaborations were established by four teams in numerous regions: Africa (Egypt, Morocco, Benin, Cameroon, South Africa, Madagascar, Burkina Faso, Algeria), Middle East (Saudi Arabia, Qatar), Asia (Vietnam, China, India), South America (Brazil, Colombia), Turkey.

"Inclusion of representatives of the more junior staff on some decision-making bodies would be beneficial."
- Progress was achieved. In 2021, Imagine launched Theme Leaders@Imagine, allowing some staff researchers to be linked to a research theme and receive greater visibility. Eleven were appointed by the SAB in 2021 and 2022. This was a late but encouraging beginning that still seems cumbersome. It could be sped up by a simple validation by the Executive committee.

"Although there is some effort for communication inside the Imagine institute, this could be improved."
- Progress was achieved. An internal newsletter was set up. "Le Café des Chercheurs" was started to provide a forum for postdocs, students and technical staff. A link "information visual exchange" was set up to share information about short- and medium-term challenges, governance, etc. It would be beneficial for the unit to set up a vulgarisation seminar series aimed at technical and administrative staff to relay the relevance and progress of the diseases studied.

"Expansion of bioinformatics, both as a core support service linked to the sequencing platform, and as a research discipline to develop methods to integrate multiple levels of data is needed."
- This was achieved. In 2018, Imagine implemented a new ICaRP called Translational Bioinformatics and Computational Decision-Support systems, led by Team 22. Its goal is to be a centre for bioinformatic tools and machine learning, and relies mainly on the expertise of three teams.

B - EVALUATION AREAS

Considering the references defined in the unit's evaluation guidelines, the committee ensures that a distinction is made on the outstanding elements for strengths or weaknesses. Each point is documented by observable facts including the elements from the portfolio. The committee assesses if the unit's results are consistent with its activity profile.

EVALUATION AREA 1: PROFILE, RESOURCES AND ORGANISATION OF THE UNIT

Assessment on the scientific objectives of the unit

The unit's scientific objectives were outstanding and of utmost relevance. The main objectives, to identify rare genetic diseases, understand, treat, valorise and train, were achieved with the identification of novel genetic disorders linked to a variety of diseases including infectious and hematopoietic cell-related, nephrotic, and developmental. The unit showed an impressive capacity to bring its findings to the clinic, by developing therapeutic options and repurposing existing drugs.

Assessment on the unit's resources

The unit's financial situation was outstanding. The unit benefited from Programme d'investissements d'avenir (PIA) money (17 M €), philanthropy and grants from public and charity sources, equal to 63 M euros in 2021. In 2021, the unit had a budget surplus of 1.5 M euros.

Assessment on the functioning of the unit

Human resources and gender parity were excellent. The institute (UMR + FCS foundation) has 591 members of which 61% are women. Data management was excellent. Human sample work was approved by the French Ministry, and clinical studies conformed to the European Commission standards. IT security was excellent. Clinical data were stored in a secure data centre not available for open access. Personal data was restricted to researchers involved in the project. The impact on the environment was small. Staff welfare was excellent.

1/ The unit has set itself relevant scientific objectives.

Strengths and possibilities linked to the context

Strengths:
- The unit organisation and facilities were outstanding.
- The dedication to rare genetic diseases was remarkable.
- The bed to bench to bed philosophy was well maintained.
- The synergy and cooperation between teams were clear.

The IHU Imagine comprises 24 teams that study rare genetic diseases with the goal of integrating patient-focused research into innovative care and technology transfer. The six integrated care research programs (Icarps) addressed by the unit are:
• Immunology/Infectiology/Gastroenterology
• Neuro-development
• Development and Cardiology
• Nephrology
• Hematology
• Translational Bioinformatics & Computer Decision Support Systems
Each ICaRP strategically combines the research teams with reference centres, national rare disease networks, and cognate hospital units.

The unit's scientific objectives were outstanding in this period. Since the current director took the helm (2016-2024), the unit's objectives were to identify, understand, treat, valorise and train. Specifically, the unit wanted to: (1) renew scientific research and increase performance; (2) integrate clinical and genomic data using bioinformatics and machine learning; (3) develop translational research and therapeutic options in terms of gene and small molecule treatments; (4) update platforms and services (pre-clinical models facilities, single cell, iPSC, organoids); (5) open Imagine up to the public; (6) provide coherence between the teams and clinical entities through the reference centres, Icarps and work packages.

The scientific and organisational results were outstanding. Its teams identified novel genetic disorders that were linked to a variety of diseases including infectious and hematopoietic cell-related, nephrotic, and developmental. The unit made exceptional inroads into understanding the pathophysiological mechanisms of these diseases that include the dysfunction of numerous signaling and developmental pathways. The unit showed a highly effective capacity to bring its findings to the clinic, by developing therapeutic options and repurposing existing drugs. The unit showed an impressive flexibility by quickly expanding its research focus to investigate key issues raised by the Covid-19 pandemic and has been astonishingly productive in this area.

Significant achievements included:
- doubling of genetic diagnostic elucidation rates (e.g. from 22+ to 45+% in intellectual deficiencies), using whole-exome and whole-genome sequencing approaches in-house or in the national context of the PFMG2025 program.

- creation or improvement of technological platforms (genomics and single -cell transcriptomics, iPSCs and organoids, AAV vectorology, clinical bioinformatics and genomics, transgenesis, zebrafish and pre-clinical models behaviour, 3-T MRI);
- development of the Dr WareHouse software to integrate clinical (APHP) and research (Inserm, UPC) data containing >900K individual files from >32 sources;
- affiliation to nineteen new Rare Disease Expert Centres (current total of 31), and two novel Departments of the GHU-APHP.centre/UPC (Clinical Bioinformatics, Federation of Genetics and Genomic Medicine);
- recruitment of four research teams;
- national success in translational research with three hospital-university research (RHU) projects (C'IL-LICO, Atraction, Coviferon);
- five ERC grants, two H2020 structuring programs as coordinators;
- novel gene therapy for sickle cell disease and beta -thalassemia;
- first molecules on the market for the treatment of achondroplasia (JCI Insights 2021 x2, Bone Res 2022);
- major discoveries concerning the role of autoimmunity and genetic deficits of the type 1 interferon pathway in Sars-Cov2 infection during the Covid-19 pandemic, different phenotypic expressions responsible for 20% of mortality, clinical trials (e.g. Science 2020 x3, Sci Immunol 2021, J Exp Med 2021, Proc Natl Acad Sci 2022, eClinicalMedicine 2022);
- industrial partnerships (labeling by the Tremplin Carnot and Carnot Institutes);
- highly successful Donors Campaign and major fund raising initiatives, including five research Chairs (Maison Dior I and II, MSD-Avenir, AXA, Geen-DS).

Weaknesses and risks linked to the context

No weaknesses detected.

2/ The unit has resources adapted to its activity profile and research environment, and makes use of them.

Strengths and possibilities linked to the context

The unit's financial situation was outstanding. The unit benefited from Programme d'Investissements d'Avenir (PIA) money (17 M €), philanthropy and grants from public and charity sources, equal to 63 M euros in 2021. Although the Covid health crisis diminished the number of grants obtained, this was offset by reserves from previous years. During the crisis, the unit focused on the core program, acceleration program and the execution of contracts as its priorities. In 2021, the unit had a budget surplus of 1.5 M euros.

Philanthropy played an outsized role in the budget, and the unit is well positioned to obtain this type of support. It launched its first Major Donors Campaign in 2021 called, "Research for each child means solutions for all," with the goal of raising 40 M in five years, and has raised 12 M € so far. Other strategies included: the funding of Chairs and MD research programs by private companies and foundations (e.g. Dior, FAMA, AXA, Colville Capital Partners, Fonds Derver, Promepar Asset Management); a collection campaign aimed at the general public; dedicated newsletters and conferences for donors. In addition, the annual Heroes charity gala with art auction (4 galas so far) raised an astonishing 8.2 M € in 2022.

Weaknesses and risks linked to the context

No weaknesses detected.

3/ The unit's practices comply with the rules and directives laid down by its supervisory bodies in terms of human resources management, safety, the environment, ethical protocols and the protection of data and scientific heritage.

Strengths and possibilities linked to the context

Human resources and gender parity were excellent. The institute (UMR + FCS foundation) has 591 people of which 61% are women, from 37 nations. The working language is English. 51% of the staff were permanent and 44% were on fixed term contracts. 7% of the personnel were administrative staff. The average age was 33 years old, with an absenteeism of 1%. Ten of the 23 teams were directed (or co-directed) by women; though four will close in the next period, all four of the new teams will be headed by women, giving a 40:60 women to men ratio at the team leader level. The gender equality index is 84/100, according to the unit. Lastly, an economic and social committee (ESC) was created in 2019 to give voice to employees in the management of the institute.

Data management was excellent. Human sample work, including hematopoietic stem cells and bone marrow cells, was approved by the French Ministry. Clinical studies conformed to the Good Clinical Practice requirements of the European Commission. Data privacy was ensured and sample numbers were randomized.

IT security was excellent. The unit has an IT charter that was signed by all employees. Data were stored in electronic notebooks and paper-based data were digitalised for archiving. Clinical data were stored in a secure data centre that is not available for open access. Personal data was restricted to researchers involved in the project. Data were backed up on a network that is housed in a secure room at the institute. The unit judged that there was adequate storage for data. Data access is restricted until publication, and results were published according to open data formats and international standards. Network security was taken care of by the IT department.

The impact on the environment was small. The unit has been acting to reduce the environmental footprint of the institute in terms of waste sorting, energy consumption, etc.

Staff welfare was excellent. The unit had strict laboratory practice rules, considering that the majority of researchers worked with human samples. In addition, a health and safety officer supported the staff in matters related to heath and waste management. Staff welfare was supported by a guidance committee in the human resource department, which offers seminars and a listening cell run by a consulting psychologist. The quality of the work environment was evaluated annually.

Weaknesses and risks linked to the context

Unit communication and decisions do not seem to reach all of the unit staff.

EVALUATION AREA 2: ATTRACTIVENESS

Assessment on the attractiveness of the unit

The attractiveness of the unit was outstanding. The unit has recruited five new team leaders in the past contract, eleven scientists with permanent position (either Inserm ordual university/hospital positions), and was successful in recruiting at the international level its future director. The unit had an excellent performance in training PhD students (98). Unit members were active in the organisation of international and national conferences (>20), and were implicated in various editorial responsibilities and institutional committees. Many members won international, European and national scientific prises.

1/ The unit has an attractive scientific reputation and is part of the European research area.

2/ The unit is attractive because for the quality of its staff support policy.

3/ The unit is attractive through its success in competitive calls for projects.

4/ The unit is attractive for the quality of its major equipment and technical skills.

Strengths and possibilities linked to the context for the four references above

The unit was active in organisation of international and national congresses (International Conference on Cilia, Flagella and Centrosomes, International Weinstein Congress, EMBO Cilia Meeting, MitoNice, 18th International Congress on Celiac Disease, etc.). There were numerous invitations or selection for oral presentations in international conferences and meetings (51), including prestigious conferences (18th International Congress on Celiac Disease, American Society of Gene and Cell Therapy (ASGCT), International Weinstein Congress).

The unit members were implicated in editorial responsibilities (eLife, Journal of Clinical Immunol, etc.)

The implication of the unit in various scientific societies (>40) was excellent, in particular in the immunology, nephrology, human genetics, hematology and development fields. Several members of the unit participated in different institutional committees (ANR CE14, CNRS Sec. 22, Inserm CSS1 …) or charity scientific boards (Dutch Kidney Foundation, Fondation Jérôme Lejeune, FRM, …).

The Imagine staff won various international, European and national scientific prises and awards, including Grand Prix, Fondation pour la Recherche Médicale, Prix Charles-Louis de Saulses de Freycinet de l'Académie de Sciences, Steinman Award for Human Immunology Research, Chevalier de l'ordre national du mérite, Prix Guillaume Delheim Collège de France, etc.). The clinicians were also successful in obtaining prestigious awards such as the Concours CCA-Inserm Bettencourt or Contrat d'Interface Hospitalier. The younger members of the unit were successful in obtaining prises and awards, including Young talent award L'Oréal-Unesco For Women in Science, competitive fellowships (EMBO short term fellowship, FRM, multiple travel awards and poster prises).

The attractivity for PhD students was excellent, including attracting foreign PhD students (111 PhD students 2017-2022). This was in part due to the high success rate of the students to doctoral contracts through the ministry, but with the financial resources of the IHU, the unit has an international PhD program that funds four international PhD student for four years, an MD-PhD program as well as a Protected Time program to support young medical doctors, and a program to fund fourth year PhD students. There are about twenty PhD degrees awarded per year. The attractivity for postdoctoral fellows was good, with 22 postdoctoral fellows recruited from 2017-2022, and another twelve recruited in 2023.

All unit staff benefited from a strong human resource department with integration (welcome package), communication (Monthly institute news), and support platforms (including innovation and valorisation department, clinical research assistance, grant office). The young researchers and engineers benefited from the YR2I association, partially funded by institute that organises a multitude of activities, including congress, seminars, professional breakfasts and social events. In addition, a dedicated bioentrepreneurship training program was set up to develop translational research and accelerate valorisation.

The international attractiveness of the unit is well established, with the successful recruitment of the future Imagine director from Chicago USA after an international call with 10/12 candidates being foreign or active outside of France. Furthermore, 22% of the unit personnel originate from more than 40 countries, including 4 group leaders. The unit has participated in the PAUSE program to welcome a Ukrainian researcher, as well as welcoming several international scientists.

During the last contract, Imagine recruited five new group leaders (1 ATIP-Avenir team and 4 IHU teams). In addition, four scientists were recruited as CRCN at Inserm, and seven scientists were recruited with dual university and hospital positions (4 MCU-PH and 3 PU-PH). Seven permanent engineer positions were obtained at Inserm, and thanks to internal funding, >20 [MJS1] CDI engineer positions were established, allowing the unit to retain technical expertise.

The unit took very good measures to promote open science and scientific integrity.

The unit was well funded by European programs, with the coordination of two Horizon Europe and the partnership in five others (EJPRD, ITN, EIC pathfinder, Eurostar-3), as well as five ERC recipients (2 consolidator grants). Overall, the unit had a high success rate (20-55%) at the French National Research Agency (ANR), as well as several ambitious transversal projects, which are national programs to create consortium to reinforce research and clinical care in the rare disease area (DIM "Gene Therapy", Devo-Decode, C'il-lico, Atraction, Coviferon). In addition, several projects benefited from national investment programs as PIA and CPER, as well as BPIFrance. Through internal funding, the unit supported four PhD and four MD-PhD students, fourth year PhD fellowships, several engineer positions, five chair positions (funded through philanthropy), cross-lab funding to encourage cross-disciplinary projects (8 projects funded between 2017-2022 between 220-375kE/project).

The unit benefits from 18 core facilities integrated to the IHU and the SFR Necker, are open to internal and external users. These core facilities are organised around four technological axes (nucleic acids, biology of the cell, in silico, in vivo), each with state-of-the art instrumentation. Each platform is headed by an operational manager has a scientific referent and a user committee. Three facilities were created during the past contract (bioimage analysis, neurobehaviour, and genome editing) to answer to the growing needs of the research teams. Several platforms were awarded ISO or IBISA labeling. Imagine participated in the funding of these platforms through equipment acquisition and human resources recruitment.

Weaknesses and risks linked to the context for the four references above

There is no weakness or risk identified.

EVALUATION AREA 3: SCIENTIFIC PRODUCTION

Assessment on the scientific production of the unit

Scientific production was outstanding. The unit published >5000 papers, with 730 in journals with excellent visibility and >330 in journals with outstanding visibility (Nature, Lancet, Science, Cell, New Engl J Med, JAMA). 30% of the articles involved the unit's team members as first, last and/or corresponding authors. The unit was a leader in the rare disease community. It had a critical mass of high-quality scientists with a common interest in genetic diseases. The scientific results had an outstanding impact on patient care. There was an outstanding integration of preclinical and clinical research activities within the Icarps. The basic science was excellent to outstanding.

1/ The scientific production of the unit meets quality criteria.

2/ The unit's scientific production is proportionate to its research potential and properly shared out between its personnel.

3/ The scientific production of the unit complies with the principles of research integrity, ethics and open science. It complies with the directives applicable in this field.

Strengths and possibilities linked to the context for the three references above

1/ Scientific production was outstanding. Between 2017 and 2022, the unit published >5000 papers, with 730 in journals with excellent visibility and >330 in journals with the highest visibility (Nature, Lancet, Science, Cell, New Engl J Med, JAMA). 30% of the articles involved the unit's team members as first, last and/or corresponding authors. 68% of the papers were published as open access. The three main Web of Science categories were immunology, genetics and heredity, and pediatrics. The main international collaborators were from the US, UK, Germany and Italy.

The most significant advances included the determination of numerous genes underlying genetic disorders, and the understanding of the genetic dysfunctions in neurodevelopment, infectious predisposition, immunity, erythropoiesis, kidney development, autoimmunity, inflammation, intestinal function, and skin. Additionally, advances in gene therapy were achieved for primary immunodeficiencies and inherited hemoglobin disorders; novel treatments were proposed for kidney disorders. six unit members were named among the highest cited researchers, according to Clarivate. In collaboration with the labex IBEID and Milieu Intérieur, the institute was involved in >70 publications on Covid-19.

2/ The research potential of the unit and its staff was excellent. All teams, services and platforms were by policy affiliated with each publication, and all human resources involved were co-authors. In addition, the unit recommends that manuscripts be sent to the department of innovation and valorisation so that the results can be considered for patenting before publication.

In this period, the unit launched two calls for theme leaders in order to give non-team leaders greater visibility. The candidate requirements were: a permanent position in Inserm/CNRS/university; management of >two full-time staff; publications as last or corresponding author, and grants in their name; agreement from their team leader. Eleven theme leaders were appointed from these calls by the SAB. Theme leaders participate in the IHU council, and they also have a small budget for travel and open access publications. They are appointed for a fixed period.

3/ The unit has followed the policy for scientific integrity, ethics and open science, according to the Singapore statement on research integrity. In 2022, the institute created a deontological council charged with the mission of educating and supporting the staff on ethical standards and scientific integrity, and alerting the institute ethics and scientific integrity officers in case of potential violations. In addition to open access publishing, the institute recommends that all results, reagents and protocols be made freely accessible after publication.

Strengths:
- The unit was a leader in the rare disease community.
- The unit had a critical mass of high-quality scientists with a common interest in genetic diseases.
- The unit had excellent access to patients, cohorts, samples and data.
- The scientific results had an outstanding impact on patient care.
- There was an outstanding integration of preclinical and clinical research activities within the Icarps.
- The basic science was excellent to outstanding.
- The commitment of the unit to teaching was commendable.

Weaknesses and risks linked to the context for the three references above

The institute seems to have reached its maximum space limit.

EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

Assessment on the inclusion of the unit's research in society

The contribution of research activities to society of the unit was outstanding, with the Carnot Institute label in 2020 to develop research partnership with the pharma sector and the socio-economic sphere. The unit deposited fifteen new patents in 2022 and had eight industrial transfers of patents during the reporting period giving rise to eight start-ups. The unit has a dedicated work package to contribute to sharing its knowledge with the general public.

1/ The unit stands out for the quality and the amount of its interactions with the non-academic world.

2/ The unit develops products for the cultural, economic and social world.

3/ The unit shares its knowledge with the general public and takes part in debates in society.

Strengths and possibilities linked to the context for the three references above

The unit is a pioneering centre for rare genetic diseases with the vision to integrate basic research into clinical practice. With the IHU, the interactions with the hospitals and clinicians are completely integrated within the unit vision.

The unit was awarded the Tremplin Carnot label in 2016 and obtained the Carnot Institute label in 2020, allowing it to set up research partnership activities with the pharma sector and the socio-economic sphere involved in health innovation. The unit hosted 5 companies through the Lab-in-Labs program to promote the emergence of new collaborations.

The unit has two funding schemes, for project maturation (12 Innogrants funded) and for the emergence of disruptive innovations (6 projects funded by the Springboard accelerator). In collaboration with Université Paris Cité, HEC Paris and Ecole Polytechnique, the unit is active in a Bioentrepreneurship program funded by the Fondation Bettencourt Schueller, which provided a cross-disciplinary perspective on biomedical entrepreneurship for students, future doctors, pharmacists, engineers, and entrepreneurs. In addition, the unit has developed an internal transversal call called "crosslab" encouraging cross-disciplinary projects within research laboratories for high-risk/high-gain innovative projects, providing initial funding

The development of products for the socio-economic word was remarkable. To capitalise on the translational potential of its research projects, the unit has set up an Innovation and Technology Transfer. The unit has a strong policy of protecting and promoting intellectual property, with an increasing number of new patent applications every year (15 new patents in 2022). The Imagine patent portfolio comprises 98 active patent families, with eight industrial transfers (licenses signed with industrial partners) during the reporting period giving rise to 8 start-ups.

Out of the eight start-ups created, Smart-Immune, Codoc, Medetia were born at Imagine and benefited from the Imagine accelerated scheme.

Through Work Package 7 "HSS and societal role of the Institute", the unit contributed to sharing its knowledge with the general public. In particular, three programs have been set up: HSS call, Science Outreach program, FAIR forum (to strengthen the links between patient associations and the teams). The role of the HSS call was to fund dedicated transversal projects with a deliverable societal/patient/caregiver impact, to contribute to the improvement of the care of rare disease patients or their quality of life. The science outreach program had science mediation activities, dedicated scientific conference, and a series of round tables for the general public. The unit has hosted over eleven events such as International Rare Disease Day, Celebrating Science, Institut Imagine FAIR#1.

Weaknesses and risks linked to the context for the three references abovet

There is no weakness or risk identified.

ANALYSIS OF THE UNIT'S TRAJECTORY

The unit is now recognised as a world leader in rare genetic diseases, and has successfully integrated clinical care, basic research and translational research in one location. The arrival of the future director, an MD-PhD who trained at Necker Enfants Malades and the NIH, and is currently Professor at the University of Chicago, primes the institute for the next phase. The new objectives will be to further move from gene discovery to function, from monogenic to polygenic disorders, and to deepen the understanding of the variations in clinical presentations for the same genetic mutation. The aims proposed for the next period are broad and ambitious.

Scientific Objectives
- Extend the study of monogenic disorders beyond germline mutations (non-coding DNA, RNA/DNA modifications, somatic mutations, splicing deregulations, gene modifiers)
- Bridge the gap from gene ID to function to treatment (AI integration of big data, organoids/organ on chip, pre-clinical models, chemical biology of identification of therapeutic targets)
- Transition from Mendelian to complex models
- Impact of microbes, diet and chemical exposures

Attractivity
- Call for new junior group leaders. As part of her negotiations with the funding bodies, the future director obtained 4-5 tenure track Chair de Professeur Junior positions. There will be international calls, competitive hiring packages, and a focus on strengthening the impact of the unit.
- Call for new senior team leaders (open to external and internal candidates)
- Federate research and treatment (make data available, host international symposiums, offer educational courses)
- Increase local interactions with other institutes in Paris

Organisation
- Foster synergy between clinicians and researchers. (create "multidimensional approaches to genetic and inherited conditions," (MAGICS): Development and Morphogenesis, Physiopathology of Major Systems, Multimodal Biomedical AI, Gene & Innovative Therapies; the MAGICs are meant to unite and criss-cross the existing Icarps)

Technology Transfer and Value Creation
- Enhance the gene therapy program (recruit a new leader in gene therapy to align with the Plan National des Maladies Rares)
- Promote education (bioentrepreneur training, chemical biology training, clinical research workshops)
- Improve clinical research and development (collaboration with Inserm and AP-HP)

In addition, the institute aims to strengthen and expand partnerships internationally. These will include: (i) European Reference Networks; (ii) international centres in genetics previously initiated by Imagine, like MRC Edinburgh (with a dual- affiliated lab, Team 19), Freiburg University, La Charité-Berlin, EPFL-Lausanne, the Belgian network, the Rockefeller University research centre, (with a dual-affiliated lab, Team 1), and the University of Chicago (facilitated by the arrival of the future director).

Lastly, the institute will physically expand in the next contract. Imagine will extend the building by about 1100 m2, a project that will take three years. The new space will foster the MAGIC on Multimodal Biomedical AI (recruit teams to accelerate data-exploring forces, host industrials and startups).

These are major goals with a broad vision. The unit is well placed to achieve at least a big portion of these goals, though it must consider the current space limitations when welcoming new groups.

RECOMMENDATIONS TO THE UNIT

Recommendations regarding the Evaluation Area 1: Profile, Resources and Organisation of the Unit

There is concern among the permanent staff (non-PI researchers, technical support, administration) that they are not informed of important decisions taken by the director and executive committee which concern them. The direction must take steps to increase communication down the line, both orally and in written form. For example, the UMR should provide written reports from its own Conseil de Laboratoire, as the Conseil de Laboratoire of the IHU do not always address all of the points important to the UMR.

Some teams are closing due to retirement or departure of the PI. The direction should take care to reassure and accompany the permanent staff as they change teams and settle in.

The technical staff members are concerned that those who depart are not replaced, causing the remaining staff to take up too much of the responsibilities. The direction might think about using some of the unit's resources to hire more people on permanent CDI contracts.

There is a general feeling that the unit has limited laboratory/office space that is already well occupied and the staff is worried about how future recruitments will integrate. The direction should keep this in mind when recruiting additional teams.

Recommendations regarding the Evaluation Area 2: Attractiveness

The unit has done a remarkable job of supporting both its fundamental and translational research. It is essential to continue this equilibrium in the future.

The procedure to become a Theme Leader seems cumbersome to the evaluation committee. As this is a popular initiative among the permanent staff, the direction may want to simplify the current procedure (e.g. validation by the executive committee instead of including the SAB).

Some junior PIs appear to need more support. The direction is encouraged to set up mentoring committees for them.

Recommendations regarding Evaluation Area 3: Scientific Production

It is important to ensure that those who direct research projects receive adequate recognition in publications as senior or co-senior authors.

Recommendations regarding Evaluation Area 4: Contribution of Research Activities to Society

Some groups have had trouble getting support from the Tech Transfer Office. As this is a priority for the unit, these lines of communication should be enforced.

TEAM-BY-TEAM OR THEME ASSESSMENT

Team 1: Human genetics of infectious diseases : monogenetic predisposition

Name of the supervisor: Mr Jean-Laurent Casanova

THEMES OF THE TEAM

The themes of the team are to unravel the genetic aetiology and immunological mechanisms for viral, bacterial, and fungal diseases. The team exploits the genetic discoveries to decipher the detailed molecular, cellular, and immunological bases of disease in a holistic manner.
During the Covid pandemic, the team reorganised its research activity successfully to unravel the genetic mechanisms of the severe forms with childhood onset as well as the autoimmune mechanism of the severe late-onset forms.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

"One recommandation was related to the act that the team did not have any grants from European or other international funding agencies".
During the last five years, the team obtained an H2020 grant.

"Another recommendation was to consider the opportunity to merge this team with that of Team 2 before the PI of that team retires, at the beginning of the next evaluation period".
This was taken into account and the two teams will join for the next period.

"Another comment was to consider the possibility to give a more visible role to the different researchers within the team, taking in consideration the size of the team and the breadth of the research field".
This recommendation was taken into account and the new structure of the team is organised in different subgroups, each of them being led by permanent researchers.

"A last comment was to try translating some of the discoveries to the clinical world, either by encouraging tech transfer activities or by engaging in clinical trials exploiting the newly identified variants".
Translation to biotechnologies is still considered by the team as difficult due to the environment of the Imagine Institute in this field.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	1
Maîtres de conférences et assimilés	3
Directeurs de recherche et assimilés	3
Chargés de recherche et assimilés	4
Personnels d'appui à la recherche	5
Sous-total personnels permanents en activité	**16**
Enseignants-chercheurs et chercheurs non permanents et assimilés	2
Personnels d'appui non permanents	5
Post-doctorants	1
Doctorants	11
Sous-total personnels non permanents en activité	**19**
Total personnels	**35**

EVALUATION

Overall assessment of the team

The team produces outstanding research in the field of Mendelian predisposition for infections of various types. Its scientific production was outstanding, including thirteen publications were published in highly cited journals (Science x4, Nature x2, Cell x5, Nat Med x2). The team's attractiveness was outstanding, with an exceptional international presence (second lab at Rockefeller University, editorial responsibilities for numerous journals, awards), and an impressive capacity to raise funds from national and European sources (14 ANR, Horizon Europe). The non-academic activities were excellent to outstanding, as the team worked with patient associations (Covid, Down Syndrome), and coordinated an RHU call related to Covid and other viral diseases. During the Covid pandemic, the team made a strong effort to build patient cohorts and address the hypothesis that severe disease in children can be associated with Mendelian pathogenic variants of the interferon system, and that proteins from the same family could be targets of autoimmune reactions in older patients with severe disease.

Strengths and possibilities linked to the context

The team is an international leader in the fields of inborn errors of immunity and human genetics of infectious diseases. It has been strongly interacting with the genetic epidemiology team, facilitating both the selection and study of human genetic variants, led by Laurent Abel. These two teams will merge for the next five years period, and will be organised into five sub-teams, each of them led two permanent researchers. They also have a strong link with the Rockefeller University through their International Inserm-associated laboratory (US funding opportunities, core facilities, post-doc candidates).

During the Covid pandemic, the team reorganised their research strategy to set-up an international cohort of patients in a remarkably short time, leading to outstanding results in the understanding of genetic and autoimmune factors for severe clinical forms in children and in older patients, respectively. Altogether, the collaborations have resulted in close links with groups from Saudi Arabia, Turkey, Qatar, Colombia, Algeria and China.

The team has an outstanding visibility and recognition and is attractive for students and postdocs. One post-doc and fifteen PhD students joined team during the last contract; they were funded through national and institute-sponsored PhD and MD-PhD fellowships, European fellowships (EMBO, Marie Sklodowska-Curie) and lab grants. The team had an outstanding capacity for raising funds from national agencies, including seven ANR as PI, seven ANR as CoPI, and a Horizon Europe project as CoPI. The team also received funding from French foundations (FRM, Fondation SCOR, Fondation du Souffle, Fondation Square/Fondation de France). The team members, and not only the leader, were invited to 285 conferences and organised many international and national meetings (e.g. Annual Meeting of the Henry Kunkel Society NYC, Annual Human Genetics in NYC Meeting, European Society for Immunodeficiencies 2024). The team leader and its members acted as editors of numerous journals (e.g. J Exp Med, eLife, PNAS, J Clin Immunol, Front Immunol), were on numerous scientific boards and steering committees (France, USA, Taiwan, Germany). All team members have won national, European and international awards (23 in all). In 2022, five team members were promoted to Unit Theme Leaders.

The team has an outstanding scientific production. The team mentors have been globally involved in 472 publications during the past term. Thirteen publications were published in highly cited journals, including four papers in Science, two in Nature, five in Cell and two in Nat Med; several reviews were also published in these journals. Specifically, the team has pursued the identification of, and mechanistic explanations for, rare genetic and immunological determinants in: fungal diseases (e.g. Sci Immunol, J Exp Med), recalcitrant warts (e.g. J Exp Med x3, Cell), epidermodysplasia verruciformis (e.g. J Exp Med x4), invasive pneumococcal and staphylocaccal diseases (e.g. Human Genet, J Exp Med x2, PNAS x2, Cell, Science), mycobacterial diseases (e.g. PNAS, J Exp Med x2, JCI, Cell x2), tuberculosis (e.g. Nat Med, J Exp Med x2, Sci Immunol, PNAS), viral encephalitis (e.g. Nat Med, JCI x2, Cell, J Exp Med x2), viral pneumonia (J Exp Med x6, PNAS, Sci Immunol x3). However, it is unclear how many PhD students published as first authors; the project leaders were oftentimes listed as first authors of the bigger publications.

The non-academic activities are excellent to outstanding. It worked with French patient associations to promote research on Covid, Down Syndrome, etc. It is coordinating an RHU call related to Covid and other viral diseases. The group leader has filed one patent. All team members are active on social media.

Weaknesses and risks linked to the context

Given the number of permanent researchers and its reputation, the team is encouraged to interact more in person with the general public, outside of its work with patient associations.

Analysis of the team's trajectory

The team's trajectory has been really impressive, demonstrating a strong capacity to adapt to new emerging diseases, such as Sars-Cov2 infection. In the next period, the team plans to focus on 4 research themes:

1) Autoantibodies against interferons and cytokines (Type I and II IFNs, IL-17, IL-6);
2) Mycobacterial diseases (tuberculosis, Mendelian susceptibility to mycobacterial disease);
3) Viral infections of the skin (Herpes viruses, skin viruses, papillomavirus);
4) Viral infections of the lungs and brain (Herpes viruses, RNA viruses).

The fusion of the Human genetics of infectious diseases wet and dry labs will allow the computational genetics work to be performed in one team. This should not change what is already happening now.

Each of the five sub-teams will be composed of 8-10 researchers, including >2 permanent researchers.

RECOMMENDATIONS TO THE TEAM

The size of the future team will be quite large and may be challenging in terms of management, in addition to the lab space for the PhD, post-docs and other members of the team.

Team 2: Human genetics of infectious diseases: complex predisposition

Name of the supervisor: Mr Laurent Abel

THEMES OF THE TEAM

The team (Team 2, dry laboratory) is associated with Team 1 (wet laboratory) to study human genetics of infectious diseases. Their projects were based on the hypothesis that infectious diseases are partly driven by human genetic and immunological determinants. Therefore, their aim was to identify genes/variants and immunological mechanisms driving the development of infectious diseases. Team 2 is specialised in computational genetics and Team 1 in experimental genetics.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

"The international outreach in terms of collaborations and patient recruitment should be continued, as it brings novelty and additional opportunities to explore human genetic diversity."
The team continued to develop a high number of international collaborations and patient recruitment in different countries (host of more than 20 international researchers; collaboration with Mc Gill University, Montreal; creation of the international Covid human Genetic Effort consortium with a cohort of 8000 patients; collaboration with Benin, Morocco, South Africa, Haïti for patient recruitment for studies on Mycobacteriae etc…)
"The organisation of the team - and in particular the close interactions with team 2 - work exceptionally well. This intercontinental and dry lab / wet lab synergy should be strongly encouraged. Special care must be taken of the transition that will occur when one of the PIs will retire, in 5-6 years."
For the 2025-2029 period, as the team leader has reached the upper age limit for direction of the laboratory, the dry laboratory will fuse with the wet laboratory to create a single team, where a PI from team 2 will supervise the dry laboratory subgroup which will be in close interactions with the different subgroups of wet laboratory.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	1
Directeurs de recherche et assimilés	2
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	1
Sous-total personnels permanents en activité	**5**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	2
Post-doctorants	2
Doctorants	4
Sous-total personnels non permanents en activité	**8**
Total personnels	**13**

EVALUATION

Overall assessment of the team

For the 2017-2022 period, the team had an outstanding publication activity in high level journals (Science Immunology, PNAS, Science, Am J Hum Gen, Cell, JEM…), outstanding funding raising capacity (3.6 M€), and very high international visibility. The team's non-academic activity was also outstanding. The team proved to have a huge capacity to quickly reorganise their projects and resources, as illustrated by their work (with Team 1) during the Covid pandemic, with a rapid constitution of patient cohorts at the international level and scientific production on genetics and autoimmune causes of Covid-19.

Strengths and possibilities linked to the context

Visibility/Attractiveness
Considering that the team is composed of two DR, one CR and one MCU-PH as permanent researchers, it was attractive for students and postdocs. Three post-docs were hired during the last contract. They were authors of one to fourteen publications (with 1 first author publication/1 publication in total, 1 first author publication/2 publications in total, and 5 first author publications/14 publications in total, respectively). PhD students (8 hired during the period) were authors of one to nineteen publications, with one to four as first author (most of PhD students published 1 paper as first author, with the exception of 1 PhD student who published four first author papers among 18 publications), which is excellent. All the trainees were involved in all fields of the projects and followed training at their entry in the laboratory.
The team had an exceptional capacity to obtain grants from national agencies (5 ANR as PI or co-PI, two ANR as partners, 1 ANRS as PI) and from foundations (2 as PI) or European agency (2 as PI or co-PI), for a total of 3 576 k€. A "Grand Prix FRM" prise (2022) was obtained by the team leader.
The very high international visibility of the team was attested by eleven invitations to scientific meetings (including NIH research meeting and EMBO conference), by editorial responsibilities of researchers (for example, the team leader was editorial board member of Human Genetics journal, USA), by numerous reviewing activities in high-level journals (JCI, JEM, journals from Nature group) and also by the fact that the human genetics and infectious diseases (HGID) laboratory (Teams 1 and 2) has a sister laboratory at the Rockefeller University in New York.
(Scientific production)
The team had an outstanding scientific production with a long-lasting expertise in computational genetics applied to infectious diseases due to bacterial infections (tuberculosis, leprosy, buruli ulcer) or viral infections (Covid-19, viral hepatitis). They also developed a methodological work in analysis of sequencing data. Overall, their work led to 234 publications during the period, with a substantial number published in leading journals (Science Immunology, PNAS, Science, Am J Hum Gen, Cell, JEM). Considering the strong association with Team 1, their results were often co-published with Team 1, and this constitutes a strength of their collaborative work. They mentioned that all the publications were in open access. Researchers of the team were also invited to write eighteen reviews in high level journals (Nat Rev Immunol, Lancet Inf Dis, Hum Genet…). Finally, all the doctoral and post-doctoral students contributed to the scientific production of the team (see above).

Non-academic activities
The non-academic activities were exceptional, with the development of seven softwares, participation to interviews with public medias (more than 150), and interaction with public associations especially during Covid-19 pandemic, participation to open days of Imagine institute.

Weaknesses and risks linked to the context

There are no major weaknesses identified.

Analysis of the team's trajectory

The team is a leader in computational genetics in the study of infectious diseases (mycobacterial infections, viral infections as viral hepatitis and Covid-19), with an outstanding scientific production (see above). Globally, the research dynamics of Team 2 is outstanding, with projects highly productive and clearly explained in the scientific point of view in the report, with the following aims: 1) study of the genetic component of mycobacterial infections; 2) study of the genetic components of viral infections; 3) methodological work in analysis of sequencing data. In addition, they adapted to the Covid-19 pandemics in a remarkable way with the creation of the international Covid Human Genetic effort consortium and production of a lot of high-level publications in this field. The team is highly connected with Team 1 devoted to experimental genetics of infectious diseases.

In the organisational point a view, the distribution of the projects among researchers of Team 2 and the way the projects are conducted and published with Team 1 were not clearly mentioned in the report.
As mentioned above, For the 2025-2029 period, as the team leader has reached the upper age limit for direction of the laboratory, the dry laboratory will fuse with the wet laboratory to create a single team, where one PI of the team will supervise the dry laboratory subgroup which will be in close interactions of the different subgroups of wet laboratory. This fusion of the two teams is for sure an excellent evolution of HGID laboratory.

RECOMMENDATIONS TO THE TEAM

No recommendation in particular.

Team 3: Embryology & genetics of malformations

Name of the supervisor: Ms Jeanne Amiel

THEMES OF THE TEAM

The team brings together medical and scientific experts in the field of inherited developmental malformations. The team is working on the molecular causes of congenital malformations and contributed to the identification of causal genes for many conditions. The team also investigates more specifically the physio-pathological mechanisms involved in three classes of malformations. Three permanent Inserm researchers conduct axes on respectively neural crest cell-derived disorders, brain-affecting ciliopathies, and craniofacial malformations. Combining whole exome or genome sequencing of patients and use of pre-clinical models or cerebral organoids, the team identified genetic causes and key pathological mechanisms involved in each class of diseases.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The main recommendation of the previous report was to address new topics with new approaches, and to expand towards non-coding genome and oligogenic inheritance as well as more functional analyses in model systems. In particular it was recommended to increase the bioinformatic expertise of the team and its interaction with other teams working on ciliopathies or in developmental biology. Even though the self-assessment document does not explicitly address how the team dealt with these recommendations, it appears that the team did follow several of the recommendations. For example, the team coordinates the RHU C'IL-LICO on renal ciliopathies involving six teams in France (2 at Imagine Institute) and obtained several grants to develop new expertise (CrossLAB Imagine) or to investigate new pathways with other teams involved in embryonic development (Axa Tête et cœur research grant, Crosslab microcephaly). In addition, the publication output during the contract indicates that the team maintained excellence in research.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	7
Maîtres de conférences et assimilés	1
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	3
Personnels d'appui à la recherche	2
Sous-total personnels permanents en activité	**14**
Enseignants-chercheurs et chercheurs non permanents et assimilés	1
Personnels d'appui non permanents	2
Post-doctorants	0
Doctorants	0
Sous-total personnels non permanents en activité	**3**
Total personnels	**17**

EVALUATION

Overall assessment of the team

The team's scientific production is excellent to outstanding, with 21 team papers published in this period (e.g. Nature Comm., J.C.I., Am. J. Med. Genet. (x4), Am. J. Hum. Genet.). Team attractiveness is very good to excellent with eight PhD students trained, but the documentation on training was difficult to assess. The team's societal impact is excellent, with a major impact on the genetic diagnosis of patients. The team has a long-standing expertise in medical genetics of embryonic malformations and is highly active in structuring research around rare diseases as part of the network of reference centres. This high national visibility is underlined by its success in coordinating important medical research networks (RHU) and in attracting national funding. The team should be careful to foster synergistic interactions between the different scientific axes to maintain its very high competitiveness.

Strengths and possibilities linked to the context

Team resources and organisation. The team's human resources are made up of experts in the genetics of developmental anomalies, with nine permanent hospital-associated positions (PUPH, MCU-PH, PH) and five Inserm researchers, three of whom are early or mid-carrier researchers, each leading a scientific axis or team. The team is part of a network of reference centres for rare diseases and JA directs the "Centre de Recherche sur les Maladies Rares des anomalies du développement" of the Necker campus. Such an effective network is highly efficient in the genetic diagnosis of patients suffering from developmental anomalies. This has led to the discovery of many disease-causing genes. The team has attracted major national funding (RHU, ANR) of at least 3.5 million euros and two of the PIs in charge of the scientific axes have obtained major national grants. The organisation and resources are excellent in relation to the team's scientific objectives.

The team attractiveness is very good to excellent. The team has trained eight PhD students (stated in the scientific production document, but only two PhD students are listed in the Excel sheet, making it difficult to follow this criterion). It is also not clear how many postdocs or technicians were trained during the period. The team is also part of an ITN PhD network. This section is difficult to assess with the available documentation.

In terms of scientific production, the team has contributed to 81 original papers, all published in high-impact journals. The majority are collaborative papers on the identification of causative genes in developmental disorders. Of the 21 papers signed as last author by team members, one can cite: Nature Comm., J.C.I., Am. J. Med. Genet. (x4), Am. J. Hum. Genet., Human Mol. Genetics, Brain (X2), Dev. Biol., Stem Cell Res. The team's work has identified novel molecular pathways involved in developmental disorders such as A-to-I editing or provided an understanding of the complex signalling function of the primary cilium during cortical development. Members of the team have been invited speakers at five international conferences and the team is very active in the French Genetics Society (56 posters at the Assises de Génétique). Taken together, the scientific output of this team is outstanding.

The team's societal impact is excellent. The team has had a major impact on the genetic diagnosis of patients suffering from serious diseases and, in addition to gene identification, is involved in the establishment of national protocols for diagnosis and care. The team also communicates with various audiences and contributes to the teaching of medical students.

Weaknesses and risks linked to the context

The team's implication in international projects is more limited in comparison to the team's important role in the national community and its involvement in international networks recruiting patients. This international criterion could be reinforced.

Although the scientific axes share common approaches and objectives, there is a risk that the three axes will not fully synergize and remain parallel projects. In particular, it seems important to keep innovating models and approaches (as already proposed for zebrafish modelling of human mutations, 2D and 3D organoids). In particular, three mid-career or young PIs are involved in the three axes and care should be taken to allow career development for each of them.

Analysis of the team's trajectory

For the next contract, the team will merge with the team led by one of the team leaders of team eleven working on skeletal dysplasias. Both teams share a common interest in the genetics of developmental disorders. The two teams are developing similar approaches and have complementary expertise. This should provide synergistic interactions such as for the study of the FGFR3 signaling pathways in primary cilia.

The merger of the two groups builds on already strong interactions between group members who have received joint fundings. Both groups are already collaborating to generate zebrafish models of human disease-causing mutations through precise genome editing and to accelerate the identification of variants that lead to craniofacial malformations.

This team merger will add a fourth focus on skeletal dysplasia to the three already present in the current team. There are some risks that the two teams will remain side by side and efforts will be needed to really mix expertise and goals in the future contract.

RECOMMENDATIONS TO THE TEAM

The team should be careful to keep synergistic interactions between research axes to remain highly competitive in the elucidation of the physio-pathological mechanisms downstream of gene identification. Care should be taken to training through research and fostering academic attractiveness.

Team 4: Human lymphohematopoiesis

Name of the supervisor: Ms Isabelle André

THEMES OF THE TEAM

The team utilises its expertise on cellular and gene therapy technology to understand human haematopoiesis and develop treatments for hereditary hematopoietic disorders. Its focus is vast, and the areas have included primary antibody deficiencies, reticular dysgenesis, post hematopoietic stem cell transplantation deficiencies, organ transplantation, and hematopoietic stem cell tracking in the context of various diseases.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

"A higher student supervision was encouraged - Given that the team had five researchers with "habilitation" to direct research, the fact that one PhD student defended in the previous period (with 4 PhD students were ongoing) was considered modest in terms of training, and only one of six postdocs had published."
In the 2017-2022 period, the PI gave special attention to the students and contractual staff in terms of future professional needs and goals, with a training plan and assistance in setting up a professional network. Staff researchers were encouraged to follow management and training courses, and discuss weekly about problems and solutions.

"The committee invited the new PI to establish and mark her leadership."
Despite a remarkably productive period for the team, the PI has chosen to explore new horizons, and the team will close before the next evaluation period.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	1
Maîtres de conférences et assimilés	1
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	11
Sous-total personnels permanents en activité	**16**
Enseignants-chercheurs et chercheurs non permanents et assimilés	2
Personnels d'appui non permanents	11
Post-doctorants	2
Doctorants	5
Sous-total personnels non permanents en activité	**20**
Total personnels	**36**

EVALUATION

Overall assessment of the team

The team showed an outstanding ability to bring the fruits of its research to patients. From 2017-2022, the team had an outstanding publication record in highly regarded journals (Nat Med, New Engl J Med, Nat Commun, Lancet, Blood), outstanding fundraising capacity (>7 M euros), outstanding international visibility, and excellent career training for students and postdocs. The team had an outstanding valorisation policy, with the creation of a start-up, participation in numerous clinical trials and patient registries, deposition of >ten patents (2 licensed), and outstanding exchanges with the general public including radio and magazine interviews. This team will not be renewed for the next evaluation period due to the departure of the PI.

Strengths and possibilities linked to the context

The team philosophy adhered to the overall strategy of the unit: start with a patient, identify the disease, understand the pathophysiology, and propose a treatment (cell and/or gene therapy) or improve the existing treatment.

The team publications were outstanding: 155 articles and fifteen reviews, with 81 articles in position 1 and 21 articles in position 2. Highly regarded papers have been published in Nat Med (3), New Engl J Med (2), Nat Commun (1), Lancet (1), Blood (5). >75% of the articles were published as open access.

The financial resources were outstanding. The team obtained 7.6 M euros for the 2017-2022 period [4x European 2.1 M, 7x national 1.4 M (4x ANR), university hospital research network RHU 656 K, regional 150K, charity 2.3 M, 3x industry 900 K (2x Dior Chairs)]. The team demonstrated an excellent evolution for raising funds, as the five permanent researchers are now autonomous and have successfully applied to a variety of grants.

International visibility was outstanding. All researchers were invited to give national and international seminars. The PI organised five international meetings. All researchers participated as experts in national (ANR) and international (EHA, ASH, ASGCT, ESGCT, FOCIS, etc.) evaluation bodies and societies. The PI and team members also initiated international patient registries (European APDS ESID, MSN).

The student/postdoc recruitment and training were excellent. The team was proactive in recruiting international PhD students and postdocs. All eight of the PhD students who defended in this period have published. All postdocs have also published.

The team gave courses at the university, mainly at the Master level. One PI organised a two-day inter-university diploma of immunopathology and a five-day Master 2 program in immunology and immunopathology.

The team had an outstanding valorisation program: eighteen industrial partnerships with six industrial partners were established, and included participation from all the researchers (6 services, 12 collaborations). The team worked closely with patient organisations and national reference centres. For example, one member was the leader of a RAC gene therapy trial, and was part of its dissemination board in charge of the communication. A second member created a European APDS EISD registry for work on activated PI3K delta syndromes, a Research collaboration agreement (Cellectis 2019-2023) and a know-how licensing agreement (Parexel-UCB Pharma 2019). Other work included a European consortium and patient associations for regulatory T cell therapy for type I diabetes, establishment of gene therapy protocols for IPEX syndrome and familial lymphohistiocytosis type 3 (with Flash Therapeutics).

The laboratory identified genes implicated in seven deficits, six of which are now included in diagnoses. Since 2017, eleven patents were filed: six are in priority phase, three in patent cooperation treaty phase, two in national phase. Two patents were issued in Europe, USA, and in other countries; one was granted a Fast Track in USA. Two patents were licensed, four were subject to a license option and one to a letter of intent. Two patents (T cell progenitor production process) led to the creation in 2017 of the start-up Smart Immune; two team members were acting CSO and CMO. Smart Immune was financed by family offices (22M€) and is incubated by Paris Biotech Santé. It has won awards (iNov BPI France 2019, I-lab 2018, WILCO 2017, W.I.T.H. 2017; nominated AP Innov 201. The company has 30 employees and has launched 5 clinical trials in Europe and USA.

The team had outstanding exchanges with the general public. The team participated in open days at Imagine. It has welcomed students from middle school to Master level. It participated in high school forums. Members participated in round tables and gave radio interviews on the radio (France Culture, 1.4 million listeners; RFI, 40.5 million listeners) and to magazines (Elle International, La Croix). It participated in patient associations (IRIS, IPOPI, Fondation Emmanuel Boussard, Foundation Day Solvay).

Weaknesses and risks linked to the context

No weakness detected in any category.

Analysis of the team's trajectory

The team's projects represent a federation of researchers contributing unique individual expertise and exploiting common tools to study aspects of human hematopoietic cell dysfunction. All of the projects were financed and benefited from adequate human resources. All led to publications. The team is a leader of gene therapy, and has wisely used this expertise to address a variety of diseases. It has also integrated itself into a number of international or European networks to advance newer topics.

The major research objectives were:
1) identification of genes and description of the physio-pathologies of primary antibody deficiencies (Haematologica 2017, J Clin Invest 2019, J Immunol 2020), reticular dysgenesis, MSN and OSM deficiencies.
2) the use of T-cell progenitors as new therapeutic tool by improving the process to increase yields and purity, the implementation of 2 clinical trials for the treatment of post-hematopoietic stem cell transplantation immune deficiency in pediatric and adult patients suffering respectively of severe combined immune deficiencies or malignant hemopathies, the production of gene corrected T- cell precursors to treat acquired immune deficiencies (J Allergy Clin Immunol 2018, Blood Adv 2019, Cell & Mol Immunol 2021).
3) the implementation of hematopoietic stem cell-based gene therapies to treat type 3 familial hemophagocytic lymphohistiocytosis (Haematologica 2018), hemoglobinopathies (in collaboration with the team 21; Mol Ther Methods Clin Dev 2018 x2, Blood Adv 2019, Haematologica 2020, Sci Adv 2020) and RAC1 deficiency (Haematologica 2021).
4) the implementation of a gene therapy program to treat diseases linked to lack of self-tolerance (IPEX syndrome (Blood 2021), and organ transplantation (Nephrol Dial Transplant 2019, J Am Soc Nephrol 2019, AM J Transplant 2020, Nat Commun 2021).
5) the exploration of human hematopoiesis through integrome and clonal tracking of hematpoietic stem cells in patients treated by gene therapies (Wiscott Aldrich syndrome, chronic granulomatous disease, beta-hemoglobinopathies) and the functional exploration of hematopoietic stem cells in disease and various conditioning contexts (Blood 2020, Nat Med 2022).

Following the departure of the team leader, this team will not be renewed. Most of the permanent researchers have made plans to join other teams at Imagine and elsewhere (Team 21, team 16, one team at Institut Necker Enfants Malades, the Clinical Investigation Centre for Biotherapy). The transition will take place in a staggered fashion.

RECOMMENDATIONS TO THE TEAM

No recommendations are needed. The committee congratulates the team for its outstanding work and wishes team members well in their future endeavours.

Team 5: Molecular mechanisms of hematologic disorders and therapeutic implications

Name of the supervisor: Mr Olivier Hermine

THEMES OF THE TEAM

The PI is the head of the Clinical Hematology Department of Necker Hospital and the projects of his team within Imagine are appropriately focussed on diseases of the blood system. These include three major themes: 1. Immunology, Oncology & Inflammation; 2. Mastocytosis, mast cell related diseases and the role(s) of mast cells in disease: 3. Normal Erythropoiesis and Red Blood Cell Disorders. Within each theme the team undertakes, basic scientific research, pre-clinical development, and translational programmes are often linked to other consortia and biotech companies.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous recommendations to this theme were:

1. To continue their highly productive program. It is advisable that, with help of the institute's leadership, the team focuses on reaching out more actively to the non-academic audience, as this may aid in developing the pre-clinical strategies.
In the past five years there has been substantial interaction with non-academic partners. The team has obtained twelve patents; they have been involved in the clinical application of newly introduced drugs; and they have contributed to worldwide collaborations in the field of blood diseases. Importantly the team provides evidence of wide-reaching communication with students and the general public.
2. Within the subgroups, leaders should be more clearly defined to keep the dynamic work of this group going.
The team includes thirteen "HDRs" sub-group leaders. These appear to be somewhat unevenly distributed with eight supervising Immuno-oncology and inflammation, one supervising mastocytosis and associated disorders, and three supervising erythropoiesis and red cell disorders. There is no guidance as to the independent role(s) of these investigators or how they interact.

3. In view of the wide range of projects, there may be a need to focus more clearly on a smaller number scientific priorities; notably, if f funding were to become more limited, prioritising among the many areas of work will be needed.
There is still a very wide range of projects. The team presents 33 projects for a total of 34 individuals which seems like a very unusual ratio. Usually a team of 2-3 (e.g. one post doc, one student and a technician) people would work on each substantial project.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	4
Maîtres de conférences et assimilés	3
Directeurs de recherche et assimilés	2
Chargés de recherche et assimilés	5
Personnels d'appui à la recherche	10
Sous-total personnels permanents en activité	**24**
Enseignants-chercheurs et chercheurs non permanents et assimilés	2
Personnels d'appui non permanents	8
Post-doctorants	6
Doctorants	18
Sous-total personnels non permanents en activité	**34**
Total personnels	**58**

EVALUATION

Overall assessment of the team

During this quinquennium, the laboratory has published >80 original articles equally distributed between basic and clinical research. Of the twelve articles chosen to represent the most important output of the lab, nine scientific publications appeared in specialised journals (e.g. Blood, Gut, J Clin Onc) and 3 clinical papers (N Engl J Med, Lancet, N Engl J Med) were published in journals for wide general audiences. The outputs reflected the overall excellent quality of the laboratory's research. These key reports contributed to advances in a very wide range of blood diseases including mastocytosis, lymphoma, leukaemia, sickle cell disease and thalassaemia. The team's attractiveness is excellent: the team leader was elected to three academies in this period (French x2, Belgian) and raised an impressive amount of funds (>6M euros). The team's societal impact is excellent, with the acquisition of patents, licences and the dissemination of research to a wide audience.

Strengths and possibilities linked to the context

Visibility/Attractivness
The team has good visibility, particularly within Europe, and its scientific leader (Pr. Olivier Hermine was elected as a member of the French National Academy of Science in 2018, the Belgium Royal Academy of Medicine in 2021 and the French National Academy of Pharmacy in 2022). He has also participated in broader international activities within his areas of expertise. The lab currently comprises 34 individual scientists at various levels. In the absence of any key to the figure summarising the "organisation" it is not possible to identify the level of each person other than four post-docs. It appears from the summary that the senior members of the theme are actively involved and recognised by the scientific community involved in research into blood diseases. The overall financial support of this theme is not clear but they have raised 6.4M euros funding from various sources over the past 6 years together with externally funded scholarships and fellowships. We scored this as excellent.
(Scientific production)
This team has produced more than 80 original articles where at least one member of the team is first, last or corresponding author, with 45 related to basic science and translational research and over 40 focused on clinical research. Of the twelve articles chosen to represent the most important output of the lab, nine scientific publications appeared in specialised journals and 3 clinical papers were published in journals for wide general audiences. These outputs reflect the overall good quality of the laboratory's research. These key reports contributed to advances in a very wide range of blood diseases including mastocytosis, lymphoma, leukaemia, sickle cell disease and thalassaemia. The group made significant contributions to understanding the pathophysiology during the recent Covid-19 pandemic. We scored this as excellent.
Non-academic activities
The team provides good evidence that they are committed to ensuring that their work has beneficial effects and impact on society and the economy. This is reflected in the acquisition of patents, licenses, and dissemination of their research output to both scientific and public outlets. We scored this as excellent.

Weaknesses and risks linked to the context

Visibility/Attractiveness
Without further discussion and explanation, this is hard to judge. In particular, it is not clear how attractive this team is to trainees and young investigators who are in the early stages of establishing their own independent laboratories. Perhaps this is not the aim of the team at Imagine. Nevertheless, it appears that all of the work is eventually supervised and receives the imprimatur of the team leader, rather than being a group of independent teams with common interests.

Scientific production
The group is very productive but falls a little short of the level of academic originality and impact that might emerge from a large group of scientists focussed on a smaller set of research questions. The topics pursued by the theme are mainly based on clinical observation including both common and rare diseases. The latter provide a unique source of research ideas. The end points of the research are both to gain insights into basic scientific principles and to develop new translational approaches to clinical problems. Looking from the outside, there appear to be too many diverse aims to enable the team to be at the cutting edge of the topics they are pursuing. There are twelve projects for fourteen researchers in Immunology, Oncology & Inflammation: there are eleven projects for eleven researchers addressing mastocytosis, mast cell related diseases and mast cells in diseases; and ten projects for nine researchers covering red cell disorders. This issue is compounded by the fact

that even within each of the three general areas of interest the projects appear quite unrelated (e.g. lymphoproliterative disorders, haemophilia and alternative splicing).

It may be of benefit to consider fewer topics and to examine each area in more depth, both from the point of view of understanding scientific mechanism and translating their findings for clinical improvements.

Analysis of the team's trajectory

The team will pursue a large number of research projects (33 listed) in the three main themes studied so far (Immunology, Oncology & Inflammation; Mastocytosis, mast cell related diseases and mast cells in diseases; Erythropoiesis and Red Blood Cell Disorders). There is no obvious hierarchy or prioritisation, and it is not explicitly mentioned whether funding for the coming years is already available for each project. The team is embedded in a complex matrix of collaborations, notably clinical, and has numerous contracts with industry.

RECOMMENDATIONS TO THE TEAM

The number of topics addressed might be reduced, be made more coherent and investigated in a deeper manner.

The tenured researchers should be encouraged to obtain more PhD students.

Members of this team, particularly younger members, should apply for independent grants to increase their sources of funding and develop their own curricula vitae.

Interaction with the society should be consolidated.

Team 6: Molecular basis of altered immune homeostasis

Name of the supervisor: Ms Gaël Menasche & Mr Fernando Sepulveda

THEMES OF THE TEAM

The team has a long-standing experience in exploring the molecular mechanisms causing severe immune disorders. The team focuses on three axes: (i) the genetics of immune disorders and the assessment of potential treatments in collaboration with clinicians, (ii) the genetic causes of severe allergic disorders and the study of granule transport in mast cells, (iii) vesicle trafficking in immune cells and actin dynamics in leukocytes of patients with immune disorders.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Maintenance of outputs in the top discipline specific journals.
The team published in several high-range journals as leader or as co-author.

Links with patient support groups should be explored.
The team established collaborations with several clinical units at Necker hospital.

Opportunities to develop relationships with pharmaceutical companies interested in treating patients with HLH should be explored further.
A treatment is currently explored with Necker clinicians for HLH patients. No transfer to industry has been carried out yet.

Only three PhD students have been supervised with no completions through the course of the last mandate. This appears to represent a missed opportunity which is worth exploring and addressing in the future.
Six PhD students completed their thesis during the last contract and two were ongoing in Dec 2022, which is reasonable considering the number of HDR (2).

Maintenance and expansion of clinical links is critical to ensure the translational impact of the work.
The team actively collaborates with several clinical units at Necker hospital.

It is critical that the group is nurtured as it moves to new, more junior leadership.
Leadership transfer seems to be accomplished in good conditions.

The group has a wonderful foundation but needs to define how it distinguishes itself from the opposition as it moves forward.
Even though the field is highly competitive, important original data have been obtained and published in high-range journals with author leadership.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	2
Sous-total personnels permanents en activité	**4**
Enseignants-chercheurs et chercheurs non permanents et assimilés	2
Personnels d'appui non permanents	0
Post-doctorants	3
Doctorants	2
Sous-total personnels non permanents en activité	**7**
Total personnels	**11**

EVALUATION

Overall assessment of the team

The team co-lead has an outstanding production level, with several publications in top-range journals, both as leader authors (Nat Comm, PNAS, Blood…) and as collaborators. (Nat Genet, Nat Immunol…). The team has an excellent attractiveness, as attested by numerous invitations to national and international meetings as well as meeting organisation, and are well inserted into their scientific network. The attractiveness in term of funding is excellent as they obtained 1.6 M€ in six years. They are connected to clinical units to investigate the genetics of rare immune diseases and allergy, and also to test therapeutical strategies based on their findings. They also deposited a patent and have translational projects, which is excellent for a team of this size.

Strengths and possibilities linked to the context

The team has a strong visibility, attested by multiple invitations of all three researchers at national and international meetings or seminars. The two PIs co-organised six national or international meetings in France, and one of them is member of the scientific committee of the French Society of Allergy and co-founder of the French Mast Cell and Basophil Club. They are reviewers for national (ANR, FHU-Prema), European (ERC, EMBO, FNRS, Czech Scientific foundation, European Hematology Association) and international (ECOS-Nord, ECOS-sud) grants, and both are editors at Frontiers Immunology. They are also members of local doctoral committees.

Team 6 obtained competitive grants from ANR (3), Labex (2) and charities (14) and international grants (3), as well as partnerships for innovation (2), mostly as coordinators. Altogether, they obtained 1 643 k€ in 6 years (274 k€/y), which is excellent for a team of this size.

Team attractiveness is also attested by the recruitment of eight PhDs, of which six were funded by the MENRT, indicating they were among the best students of the Ecole Doctorale. They also hired five postdocs, providing a good support of young researchers to the team.

Team 6 publication level is outstanding, with three articles in top-range journals (Cell Discovery as leader authors, Nat Genet and Nat Immunol as co-authors), five in J Allergy Clin Immunol (as main authors or co-authors), two in Nat Comm, one in PNAS, and others in high-range journals (Blood, Allergy, Haematologica, Am J Hum Genet,

Clin Immunol…). Altogether, 36 original articles (12 as main authors), four reviews and two book chapters were published, demonstrating their capacity to publish their own results, and their achievements as collaborators.

Team 6 developed clinical trials based on their own findings in basic research. In 2017, Team 6 deposited a patent on inhibitors of mast cell degranulation. Since then, they have identified new targets to inhibit granule secretion by mast cells. They also started a new translational project by the use of antisense oligonucleotide to treat allergy, which is supported by Inserm Transfer and by Imagine Innovative and technology department with a CoPoc and an Innogrant. In collaboration with clinicians at Necker hospital, they also brought a proof-of-concept for a new treatment for SPTCL and HLH patients.

Weaknesses and risks linked to the context

The main weakness is related to the PhD students. PhD students stayed four years in average in the team (two stayed 5 years), which is longer than the recommended three years. Their publication level is low: 1.7 original article per student with defended thesis and 0.5 per student as first author.

Similarly, postdoc publication level is very low (two without publication and two with no publication as first author).

Outreach to lay public is limited.

Analysis of the team's trajectory

All permanent members will remain in the team, which will stay in Imagine unit. The scientific projects will be in continuation with the previous projects and they are divided in three axes: 1/ the genetics of non-classical forms of HLH, 2/ the identification of new molecular determinants of allergic disorders and 3/ cytoskeleton dynamics and vesicular trafficking in leukocytes migration. All three projects are founded and have potential therapeutic benefits. Altogether, team projects are ambitious, but their number is high for a small team.

RECOMMENDATIONS TO THE TEAM

The committee recommends to pursue this excellent level of production both in basic and translational research.

We also recommend to make efforts to increase the publication level of PhD students and postdocs and to limit their stay in the lab.

More effort of outreach to the general public should be made.

Team 7: Immunogenetics of pediatric autoimmune diseases

Name of the supervisor: Mr Frédéric Rieux-Laucat

THEMES OF THE TEAM

The main hypothesis pursued by the team is that "the occurrence of early-onset autoimmune diseases is associated with a monogenic predisposition". They are interested in particular by mutations of the FAS gene causing ALPS, identification of genetic defects in pediatric Evans Syndrome, and early-onset Systemic Lupus erythematosous (pSLE). The latter studies led the team to discover pathophysiological mechanisms of severe Sars-CoV2 infections in adults and children.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous report was highly elogious and made no specific recommendations to the team. The experts identified as potential threat the fact that the most obvious monogenic mutations may soon all be found and therefore conducting high level research in this competitive field might become more difficult. In its trajectory, the team has responded well to this potential threat (see below).

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	3
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	2
Sous-total personnels permanents en activité	**8**
Enseignants-chercheurs et chercheurs non permanents et assimilés	4
Personnels d'appui non permanents	0
Post-doctorants	7
Doctorants	15
Sous-total personnels non permanents en activité	**26**
Total personnels	**34**

EVALUATION

Overall assessment of the team

A major strength is the constitution of large patient cohorts in collaboration with other local, national and international institutions: This major effort is paying off by allowing rapid progress and leading to publications in top journals. Especially the contribution to understanding the pathology affecting severe Covid-19 patients is very impressive. The team is evaluated as Excellent to Outstanding for Attractiveness, Outstanding for Scientific Production, and Excellent to Outstanding for Outreach.

Strengths and possibilities linked to the context

Evaluation area 1: Profile, Resources and Organisation of the Team
The scientific profile is perfectly in line with the goals and missions of the Imagine Institute and is quite impressive in its breadth and depth. In all cases presented, the team has been able to identify the pathophysiological consequences of the mutations discovered, characterise signalling pathways involved and to test potential treatment options. In addition to its core projects, the team has made two very significant contributions to the understanding of severe forms of Sars-Covid-19 in adults and in children.
Financial resources are plentiful, even in the absence of European funding, and include 5 highly competitive ANR grants, as well as funding from industry covering clinical trials. Applications are in preparation for two ERC grants and a Horizon 2020 grant.
Evaluation area 2. Attractiveness
Team members are actively involved in European scientific and clinical institutions and are frequently invited as speakers to international conferences. The team is able to attract excellent students and scientists and provides them with high-level training.
Evaluation area 3. Scientific production
The self-evaluation report mentions 10 articles in journals with top impact factors and the publication list in the Annexe lists 544 entries, mixing everything from peer-reviewed articles to conference contributions. It is neither in alphabetical nor in chronological order, lists only some authors (not even the last author) and fails to include volume number and page number, making it impossible to evaluate the output of the team within a reasonable amount of time. There is no doubt that the team is highly productive, but such a publication list is unacceptable. Further information given at the site visit indicates 286 original publications, of which 58 with first or last authorship from team members (24 classified among top 10 in numbers of citations). Top publications selected by the team were published in Science and Nature Communications. In addition, leading journals include Clinical Haematology, Blood and Journal of Allergy and Clinical Immunology.
Evaluation area 4. Contribution of Research Activities to Society
In addition to important collaborations with the pharmaceutical industry, the self-evaluation report lists two patents and a number of activities designated to disseminate scientific knowledge (and know how) in society.

Weaknesses and risks linked to the context

Evaluation area 1: Profile, Resources and Organisation of the Team
The self-evaluation report focusses on the scientific profile of the team, but fails to describe the team, making it difficult before the site visit to evaluate how the team is organised and how it functions. It is not indicated who is responsible for which projects and how PhD students and Postdocs are involved. These issues have been clarified.
Evaluation area 2. Attractiveness
The very small number of postdocs (1 listed in the table above) and PhD students (about 1 recruited/year) is surprising. However, the presentation at the site visit listed a much higher number of students and postdocs, distributed among the three main research units of the team.
Evaluation area 3. Scientific production
No weakness noted.
Evaluation area 4. Contribution of Research Activities to Society
Given the size of the team, public outreach activities aiming at knowledge dissemination could be intensified.

Analysis of the team's trajectory

The team has made seminal discoveries of monogenic predisposition to pediatric autoimmune diseases and has unravelled the function of major mutations. However, it has recently observed that mutations are not always a good predictor of disease symptoms. Understanding which additional factors or modifiers are involved will be a major aspect of research planned for the coming cycle. Among the factors considered are somatic mutations, epigenetic modifications and infections. To this end, dysregulations at the transcriptomic level will be analyzed by single cell RNA sequencing.
The team lists seven major projects, which represent a logical continuation of on-going work and are based on available competences with respect to multi-omics technologies. Some of these projects are rather challenging but might lead to real progress and therefore be considered "high gain" projects.
Of concern is that the self-evaluation document remains rather vague on timeline, milestones, or criteria for prioritisation.

RECOMMENDATIONS TO THE TEAM

Considering that the team leader will retire after the end of the next contract, we strongly recommend to plan ahead to ensure completion of ongoing projects and continuity with the new leadership.

Team 8: Genetics of mitochondrial diseases

Name of the supervisor: Ms Agnès Rötig

THEMES OF THE TEAM

The team research is divided into six research axes around the genetics of mitochondrial diseases: pre-clinical model for mitochondrial and metabolic diseases and gene therapy; Mitochondrial diseases and interferon response; Mitochondrial DNA segregation during embryo-fetal development; Iron homeostasis in Friedreich ataxia and NBIA; Genomics and transcriptomics for gene identification; Reference Centre for Mitochondrial Disorders.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

"The previous recommendations from Hcéres did not include any major directives but underscored the importance of enhancing the popularisation of scientific information. They also suggested a strengthened focus on the physio-pathological aspects and mechanisms related to the disorder. Recruiting new researchers with expertise in pathophysiology was highlighted as a key consideration".
All these recommendations have been addressed.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	4
Maîtres de conférences et assimilés	1
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	3
Personnels d'appui à la recherche	4
Sous-total personnels permanents en activité	**13**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	2
Post-doctorants	1
Doctorants	5
Sous-total personnels non permanents en activité	**8**
Total personnels	**21**

EVALUATION

Overall assessment of the team

Overall, the team as an excellent to outstanding scientific production with the identification of eight novel genes causative of mitochondrial disorders and with 69 publication with some in leading journals. The attractiveness of the team is excellent, with three postdocs, six PhD students and recruitment of four permanent scientists. The outreach activity is very good, with two patents and connection with patient association.

Strengths and possibilities linked to the context

Visibility/Attractiveness
The team has an outstanding visibility and recognition in the field of genetics of mitochondrial disease. It is very attractive for students and postdocs. Three post-docs were hired during the last contract, six PhD students and several master students. Five PhD students were authors of one-ten publications, among which one-two as first author. One PhD student has two publications in preparation, with one as first author. The publication record of the PhD students is excellent. The team has a strong capacity to lead research projects with four full-time tenured researchers (1 DR1 and 3 CRCN). In 2021, the team has attracted a new Inserm CRCN scientist which brought the expertise in the field of pre-clinical models. In addition, five medical professors with clinical or teaching duties are part of the team, including the members of the translational genetics plateform. The team has a very good capacity to obtain grants from Europe (E-rare 2015, EJP-RD 2019, ERA PerMed 201), national agencies (Aviesan, Rare Diseases, DIM Thérapie génique) and from charity associations (AFM, AFAF, POLG Foundation). The outstanding international visibility of the team is attested by 22 invitations to scientific meetings, including prestigious conferences (EMBO Workshop, Cold Spring Harbor Laboratory, European Society of Human Genetics, ESHRE) and by organising four international scientific meetings (ENMC workshop,MitoNice, 2 NBIA conferences). Four members of the team are involved in research steering bodies (such as Coordinator of Cellule Recherche de la Filière Nationale de Santé des Maladies Héréditaires du Métabolisme (G2M), Governing board of the Code Biology Society, Member of the scientific committee of Fondation Jérôme Lejeune, President of the SSIEM, or Comité d'éthique de l'Inserm)
Scientific production
The team has an excellent scientific production with a long-lasting expertise in identifying novel genes whose mutations cause mitochondrial diseases (8 novel genes), novel mutation in genes linked to mitochondrial diseases, in identifying the pathogenesis in neurodegeneration with brain iron accumulation (NBIA) and in prevention of mtDNA disordres. More recently, the team has developed expertise in gene therapy and pre-clinical models for mitochondrial diseases. The team has a total of 69 publications, with nineteen publication as first/last co-authors, one publication as first author, one publication as last author, and two publications as co-last author. Some of these publications are in leading journals (Nat Comm, AJHG, HMG, Blood, Neuromuscular Dis.). In addition, due to the very few patients per disease, international collaboration is very active (50 publications). All team members contribute to the publications.

Non-academic activities
The non-academic activities are very good with one patent application (Treatment and prediction of therapeutic responses in patients suffering from Friedreich ataxia (1000490688) in 2019) and one patent Gene therapy for Maple Syrup Urine Disease (WO2021170784A1) in 2021. Since 2019, the team has a collaboration with a biotech (Moderna Therapeutics) to develop mRNA therapy for Maple syrup urine disease. The team is a member of the Carammel clinical reference centre and has strong links with patient associations (AMMi). Team members are involved in communication to the general public on gene therapy, mitochondrial disease and genetic test through conferences (5), roundtable (1), press conference (1) or radio (1 France Inter).

Weaknesses and risks linked to the context

Visibility/Attractiveness
While the team is extremely successful in obtaining European and national grant as well as grant from charities, surprisingly, no grants from the National funding agency ANR have been obtained.
While 22 invitations to conference are impressive, this corresponds only to two senior researchers. Few younger members present their work at selected talks.

Scientific production
No weakness

Non-academic activities
Although on patent has been approved, it has not resulted in licensing. Considering the translational capacity of the research of the team, increasing collaboration with biotech would help move some treatment forward to clinic.

Analysis of the team's trajectory

The team leader will be replaced for the next mandate starting 2025, however, the new leader has not clearly been identified. The strategy to recruit a new leader should be specified. While it is stated that new projects will arrive with the new team leader, and some projects will be stopped, it is not clear from the report which projects will be stopped.
From the team 9 report, it is stated a temporary change, and that the team has considered 1) joining the team 9, 2) recruiting, with the help of the SAB, new young researchers for a high level and innovative basic science

research, 2) contributing to the creation of a novel "Gene therapy" ICARP which would host the gene therapy projects.
The trajectory is capitalising on the strength and expertise of the team members, from the patient database and gene identification, pathophysiological of NBIA and FA, gene therapy for three mitochondrial disease and mtDNA heteroplasmy and development.
The feasibility of the outlined approaches would be convincing if it was for the next contract, but is too ambitious for 2023-2024.

RECOMMENDATIONS TO THE TEAM

- Increase the funding sources through applications to the ANR.
- Promote the younger researchers to be invited to conferences.
- Increase collaboration with industrial partners
- Urge to find a new team leader or to integrate the different projects in relevant teams

Team 9: Genetics of ophthalmologic, auditory and mitochondrial diseases

Name of the supervisor: Mr Jean-Michel Rozet

THEMES OF THE TEAM

The scientific objectives of the research team aim to: (i) Identify new genes in rare hereditary visual disorders and unravel new mechanisms; (ii) Develop new diagnostic tools and biomarkers for personalised diagnosis and prognosis; and (iii) Develop innovative therapeutic approaches.
The strategy implemented builds on a multidisciplinary approach that combines clinical genetic, exceptional cohorts of well-characterised patients, multiomics approaches as well as pathophysiological and therapeutic research.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

"*Previous recommendations from the Hcéres committee to IMAGINE Institut suggested reinforcing patient-centreed research and state-of-the-art omics approaches*".
The research strategy developed in team 9 is already aligned with these recommendations, as it focuses on integrated research strategies. These strategies combine patient-centreed approaches, starting from presymptomatic markers to improving outcomes and prognosis, while also dedicating efforts to therapeutic approaches. Moreover, the team appears to already implement state-of-the-art omics techniques, including whole-genome sequencing.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	1
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	2
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	2
Sous-total personnels permanents en activité	**6**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	0
Post-doctorants	1
Doctorants	5
Sous-total personnels non permanents en activité	**6**
Total personnels	**12**

EVALUATION

Overall assessment of the team

The team has demonstrated outstanding scientific production, as evidenced by publications in excellent journals and licensed patents. The outreach is outstanding with a solid translational research provides patients with excellent clinical and genetic testing, as well as promising therapeutic opportunities. The attractiveness of the team is excellent.

Strengths and possibilities linked to the context

The team's long-standing activity, has endowed it with extremely strong national and international visibility, forming partnerships with high-profile institutions. During the last 2017-2022 contract, the team was a relatively small yet highly effective group given its outstanding scientific visibility and recognition in the field of genetics of visual disorders.
Three Ph.D. students successfully defended their theses and collectively published six papers as first authors. The team has a strong capacity to lead research projects with three full-time tenured researchers (1 DR, 1 DRE Emeritus and 2 CRCN). In addition, he team's excellence has resulted in the significant achievement of securing 28 grants, totaling over 1.6 million euros, from various national funding agencies(n=6), associations/foundations (n=14), and industries (n=3). Part of these funds were allocated to Ph.D. and postdoc fellowships. The outstanding visibility allowed them to contribute to fifteen international and eleven national scientific meetings, along with 38 selected oral presentations and 129 posters.
Last, the Prix de la Fondation de l'OEil awarded to I. Perrault in 2019 *illustrates the excellent visibility of the team*.

Scientific production

In the current contract, the team has continued to build on their previous outstanding achievements in identifying novel genes in visual disorders and understanding the underlying pathophysiology.
During the 2017-2022 period, the team has contributed to 42 publications, with at least seventeen as first/last or corresponding authors. Several of these publications are featured in leading journals in their specialty, including JCI, Blood, EMBO Molecular Medicine, American Journal of Medical Genetics Part A, Brain, and the American Journal of Human Genetics. Additionally, a major paper with both first and last co-authored by team members is currently in revision at the Science journal. 3 invited reviews complete the portfolio.
Altogether the Scientific production is excellent to outstanding.

Non-academic activities

The team has filed a total of eight patents, among which two have been licensed since 2018. These licensed patents have facilitated Phase 1/2 and ongoing Phase 2/3 clinical trials.
Furthermore, the team actively participates in the drafting of standards on both clinical (care protocol on aniridia e.g.) and scientific (member of the expert panel of the NIH Clingen to draft standards of variant interpretation). Additionally, team members participate in Boards and/or Scientific and Medical Advisory Boards of seven Patient Associations and Foundations in France and abroad.
Altogether the Non-academic activities is outstanding.

Weaknesses and risks linked to the context

Visibility/Attractiveness

According to the report on team 8, it is mentioned that she will be replaced for the upcoming mandate starting in 2025. However, a new leader has not been clearly identified yet. While awaiting the appointment of a new team leader, members of team 8 are being considered for integration into the team 9. This uncertainty poses potential concerns for team 8 members. It is advisable to establish transparent communication channels to ensure the effective dissemination of information.
Clearly outline the short to mid-term perspective for team 8 within the hosting context.
Organise Q&A sessions or open forums to allow staff to express their thoughts and seek clarification.
Implement regular check-in meetings with both teams
Provide a positive and collaborative working environment to avoid unnecessary anxiety.

Scientific production
The team does not show any significant weaknesses. However, it is worth mentioning that finalising and publishing several manuscripts in preparation is crucial, especially for the students. A slight decrease in publications in top journals (e.g., Nature Genetics) is noted, but the team's state-of-the-art multidisciplinary approaches are expected to pave the way for new ground-breaking discoveries in the field.
Non-academic activities
No major weaknesses.
Despite having a remarkable team, there are few or no international contracts. It's worth noting that the team has actively responded to international calls, but securing more international contracts could further enhance their global collaborations and visibility.

Analysis of the team's trajectory

In the next contract, the team will encounter two significant changes. First, the team will undergo a permanent change and expand by hosting two new researchers (1 MD, PhD, PH, and 1 CR1) with whom the team has

successfully collaborated in the past years on rare conditions presenting with both vision and sensorineural hearing loss. Second, and as previously mentioned in the 'risk' section, the team will experience a switch by hosting team 8 (Genetics of Mitochondrial Disorders), with whom they have had a longstanding collaboration on HONs. This decision follows the departure of the team leader of team 8 (likely retiring during the next mandates) while waiting for the recruitment of a new PI by 2025. The temporary merge is not expected to jeopardize or weaken team 9 and will ensure a smooth transition before the recruitment of a new PI for the Genetics of Mitochondrial Diseases team. Fruitful active scientific collaborations exist in the current mandate between the two teams. The strategy is excellent and is a continuation of the research that has been conducted during the previous term, with cutting edge genetics and bioinformatics research project guaranteed by the track records of the team and the availability of an outstanding collection of patients, families and control samples, a high throughput NGS platform and mathematical and informatics expertise.

Notably and quite intriguingly, certain research projects undertaken by the team have resulted in the identification of pathways and genes that may play a role in common diseases, such as glaucoma. Furthermore, their investigation into congenital microcoria (MCOR), a rare autosomal dominant malformation of the iris and a significant risk factor for optic nerve damage, is paving the way for a promising research field. Finally, and importantly, the team is dedicated to enhancing outcome prognosis and identifying pre-symptomatic markers of extraocular involvement.

Altogether, the trajectory of the team is well structured and ambitious. It capitalises on the strength and expertise of the team members and masters all aspects of the project. The thematic area and distribution of forces are well balanced and will be organised

RECOMMENDATIONS TO THE TEAM

Building upon the scientific excellence achieved during the current mandate, the committee expresses confidence that the team is poised to continue flourishing. The team is anticipated to further advance the comprehension of rare ophthalmic conditions, with a paramount focus on delivering impactful translational science.

Team 10: Laboratory of Hereditary Kidney Diseases

Name of the supervisor: Ms Sophie Saunier

THEMES OF THE TEAM

The team has long-standing expertise in the field of hereditary kidney diseases. It brings together experts in various fields of investigation, from clinical to genetic diagnosis, basic research and therapeutic approaches. The team focuses on several kidney disorders involving different regions of the nephron or affecting kidney development. In particular it addresses the genetic and physio-pathological mechanisms involved in nephronophthisis, renal hypodysplasia, steroid resistant nephrotic syndrome and cystinosis. The team integrates genetic diagnostics, advance fundamental research using cell systems (organoids, URECs) or pre-clinical models and develops therapeutic screens and strategies to treat these diseases.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

"*There were no major recommendations in the previous evaluation other than to maintain excellence by capitalising on their unique expertise and to be vigilant in organising team management given the increasing number of projects*".
In agreement with these recommendations, the team has been very successful in achieving its objectives during this contract, maintaining its excellence and attractiveness, and pursuing the implementation of new projects, approaches and networks.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	2
Maîtres de conférences et assimilés	2
Directeurs de recherche et assimilés	2
Chargés de recherche et assimilés	3
Personnels d'appui à la recherche	6
Sous-total personnels permanents en activité	**15**
Enseignants-chercheurs et chercheurs non permanents et assimilés	3
Personnels d'appui non permanents	8
Post-doctorants	3
Doctorants	3
Sous-total personnels non permanents en activité	**17**
Total personnels	**32**

EVALUATION

Overall assessment of the team

The team is outstanding in scientific production, attractiveness and societal impact. The team's strengths lie in its ability to bring together medical and basic science experts, and to constantly develop new approaches to overcome scientific obstacles. It has made notable contributions in uncovering new pathological mechanisms in kidney diseases, such as inflammation and the contribution of RNA modifications, opening up new therapeutic options. The team is internationally recognised, excellent in fundraising, networking and highly attractive. The scientific output is outstanding.

Strengths and possibilities linked to the context

Team resources and organisation
The team comprises core permanent researchers with diverse expertise, facilitating an integrated research program perfectly aligned with the Imagine Institute's objectives, spanning molecular diagnosis, understanding of physio pathological mechanisms, and exploration of potential therapies. The team secured eighteen grants, totalling seven million euros from local, European, and industrial sources. These funds facilitated the recruitment of tenpostdocs, three PhD students, and fifteen engineers, essential for developing innovative models and methods (such as pre-clinical models, organoids or usage of antisens oligonucleotides). Team efforts are also dedicated to supporting early-career researchers and fostering career growth across the team.

In terms of attractiveness, the team trained fifteen Master 2 students and fourteen PhDs. Seven PhDs were supported by the BioSPC doctoral program (indicative of highly competitive recruitment) two by Pasteur-Imagine international PhD program and two from an ITN european network (SCILS2). Additionally, twelve postdocs were trained, with eight securing positions in biotech companies and one obtaining a permanent CNRS position. The outstanding team's appeal lies in its success in highly competitive calls leading to high funding levels or intensive networks (for example Marie Curie ITN, RHU C'IL-LICO, Horizon Europe Work programs, and Predict) and its excellent scientific and technical environment. Last, members of the team are also actively involved in numerous scientific committees or boards (section 22 CNRS, CSS1 Inserm, scientific committee of Inserm, ANR committee…). C. Antignac was elected member of the Académie des Sciences in 2019.

Regarding scientific output, the team contributed to 60 original articles and four reviews. Notably, the 26 original articles signed by team members as last author were published in high-impact journals like Nature Genetics, Nat. Comm., Am. J. Hum Genetics (x3), PNAS, JCI, Human Mol. Genet. (x4), and PLoS Genetics, with two patents resulting from the team's research. Team members also delivered 60 oral presentations (36 by invitation), presented 23 posters, and authored 1 book chapter. Additionally, 146 publications were published by clinicians associated with the team. Collectively the scientific productivity of the team is outstanding.

In terms of societal impact, the team is highly engaged in various initiatives addressing societal challenges. This includes active involvement in teaching across medical and scientific tracks in Paris and also Shanghai, knowledge dissemination to diverse audiences (high schools, patient associations, general public), and collaborations with industrial partners like Alexion R&D France and Medetia. Noteworthy projects include the development of therapeutic agents for NPH (leading to two patents) and creating informative materials for children and their parents affected by NPH in collaboration with AIRG.

Weaknesses and risks linked to the context

There are no major weaknesses identified. The strategy to develop novel therapeutics is certainly of high risk but perfectly anticipated by the team with several private partnerships and scientific networks.

Analysis of the team's trajectory

For the next contract, the team will continue to pursue its research priorities, building on the significant funding already secured and the young researchers recruited, who are an important asset in maintaining innovation. Along the genetic axis, the team aims to identify causative rare variants of known genes and modifier alleles that may be responsible for clinical variability. This is a major challenge in the field and requires novel sequencing (WES/WGS combined with bulk and target RNA seq) and analysis pipelines. In a second axis, the team will continue to unravel the pathophysiological mechanisms involved in renal-associated diseases by developing novel lines of research, tools and models. In particular, the team aims to understand the contribution of RNA metabolism dysfunction in Galloway-Mowat syndrome, to identify novel markers of disease progression and to gain a comprehensive understanding of the role of inflammation in NPH. In the third axis, the team will increase efforts to develop novel therapeutic strategies, either through pharmacological screening or gene design therapies (RNA-targeted therapies or AAV therapy). This axis is based on several partnerships with private companies and is gradually becoming a major part of the team's projects.
Together this is a well-structured and ambitious project.

RECOMMENDATIONS TO THE TEAM

The committee can only recommend to keep its high standard of scientific achievements and excellent team management.

Team 11: Molecular and physiopathological bases of osteochondrodysplasia

Name of the supervisor: Ms Laurence Legeai-Mallet & Ms Valérie Cormier-Daire

THEMES OF THE TEAM

The team is composed of two groups, each headed by one of the two co-PIs. The team has a long-standing expertise in the ossification processes using skeletal dysplasia (SD) cellular and pre-clinical models. Its main objectives are 1) the identification of novel genes and novel mechanisms, using integrative OMIC approaches, 2) focusing on SD related to an extracellular matrix impairment to understanding their physio-pathological bases 3) developing novel therapies targeting TGF signalling and GAG synthesis or achondroplasia and hypochondroplasia, 3) deciphering Fibroblast Growth Factor signalling and bone diseases using molecular, cellular and transcriptomic analyses using relevant human cellular lines and zebrafish and pre-clinical models.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

In the previous report, it was recommended i) to continue with their successful strategy to identify and study skeletal disease pathology ii) to pursue the cooperative approach towards this complex medical/biological problem iii) to focus more on the molecular pathology and treatment development of certain selected conditions and iv) to obtain support (sequencing, bioinformatic analysis, access to novel technologies such as single cell sequencing) possible from the Institute in particular related to the analysis of so far unsolved cases.
The team has indeed followed most of these recommendations.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	2
Maîtres de conférences et assimilés	5
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	7
Sous-total personnels permanents en activité	**16**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	4
Post-doctorants	9
Doctorants	7
Sous-total personnels non permanents en activité	**20**
Total personnels	**36**

EVALUATION

Overall assessment of the team

The team is internationally recognised and plays a major role in the understanding of ossification process and rare related diseases, which leads to develop original therapeutic strategies for bone disorders. The attractiveness of the team is excellent as they attract numerous students and scientists (9 Post-docs, 7 Research assistants, seven PhD students, one CRCN recruited) at Inserm during the evaluated period. The scientific production is excellent to outstanding with 130 publications, in leading position for one third of them. Some were published in highly-reputed generalist (e.g. Nature, Nature Comm, Nature genetics). The scientific output is outstanding with ten patents (one licensed), several collaborations with the pharmaceutical industry, disseminations of scientific knowledge to the general public and numerous communications with patient associations.

Strengths and possibilities linked to the context

The team benefits from a close link with the Reference Centre for Skeletal Dysplasia and the complementary expertise of its members (scientists and clinicians) constitutes also a great opportunity. Thus, the team combines very efficiently the analysis of data from patient samples and valuable information provided by the generation of specific human, pre-clinical models they develop.
The team has contributed to the identification of the molecular basis of more ten skeletal dysplasia combining next generation sequencing analyses and functional studies using in-house generated cellular or pre-clinical models. They have developed numerous preclinical studies for achondroplasia which are now in active clinical development. As a proof-of-principle study, they found that the phenolic compound (-)(-)-epicatechin is a potential drug for the treatment of achondroplasia. These results have obtained the support from the Springboard, Imagine Institute's accelerator for the creation of a start-up. Importantly, the team is heading the French reference centre for skeletal dysplasia (CRMR-MOC)
Evaluation area 1: Profile, Resources and Organisation of the Team
The team was extremely successful for obtaining external funding (~7 M € coming from International and European grants (Cofecub, 1 H2020, 1 MSCA-DN), national grants (3 ANR grants as Project Leader), patient associations or foundations (17 grants) and private companies (17 contracts).
Evaluation area 2. Attractivenes
Team leaders are involved in international learned societies ('Basic translational chair of European calcified tissue Society, President of European Society of Human Genetic) and in national advisory boards of pharmaceutical companies or patient groups support. With more than 80 conference invitations as speakers, as well international (~50, e.g Gordon conferences) as national conferences (> 30), the team is highly recognised in the skeletal dysplasia community.
The team is able to attract excellent students and scientists (9 post-docs, 7 Research assistants, 7 PhD students) and provides them with high-level training. Three team members were promoted as PU-PH during the period and one was recruited as CRCN at Inserm. The team attractiveness is excellent to outstanding.
Evaluation area 3. Scientific production
The production is excellent to outstanding. The team has co-authored more than 130 publications, has been in leading position for one third of them. Most were published in highly-reputed generalist (e.g. Nature, Nature Comm, Nature genetics) and specialised journals (e.g Bone research, Brain). These publications also illustrate the strong international network to which the team contributes.
Evaluation area 4. Contribution of Research Activities to Society
The team has developed ten patents. One patent is licensing. It collaborates with the pharmaceutical industry. It disseminates scientific knowledge to the general public using different media (e.g. podcasts) and is particularly involved in communicating with patients associations. Overall, its contribution is outstanding.

Weaknesses and risks linked to the context

The team will split for the next contract. The risk is to lose the complementary expertise and a part of the international network built by the co-PIs.

Analysis of the team's trajectory

The team will close at the end of the present contract and each PI will join a different team. The trajectory is evaluated in the context of their new teams.

RECOMMENDATIONS TO THE TEAM

No recommendation

Team 12: Developmental brain disorders

Name of the supervisor: Mr Vincent Cantagrel

THEMES OF THE TEAM

The research team is investigating Developmental Brain Disorders (DBD), which represent a highly heterogeneous group of diseases. These disorders are characterised by impairments in cognition, communication, behaviour, or motor functioning resulting from atypical brain development. Within this broad spectrum, the group encompasses various conditions, including Intellectual Disability (ID), Autism Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorder (ADHD), Specific Learning Disorder, and Motor Disorders. Notably, neurodevelopmental disorders can extend beyond these categories to include conditions like schizophrenia and epilepsy. The underlying pathophysiological mechanisms for DBD are conceptualised as a continuum of developmental brain dysfunction.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

"The previous committee's primary focus was on the imperative need to recruit additional permanent staff members and ensure minimal negative impact following the leadership change at the inception of the last contract".
It is gratifying to note that, considering scientific production and grants obtained during this period, these concerns have been effectively addressed.
"*Another specific concern revolved around the dedicated work on cerebellar development, requiring increased collaboration with specialised teams studying the interactions of the cerebellum with other brain regions to comprehend its contributions to behaviour*".
This concern has been attentively tackled through the recruitment of a CRCN Inserm, specialising in the neurodevelopment mechanisms of the cerebellum. Additionally, the inclusion of a clinician responsible for the national reference centre for congenital cerebellar defects further reinforces their commitment to this area of research.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	1
Maîtres de conférences et assimilés	1
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	2
Sous-total personnels permanents en activité	**7**
Enseignants-chercheurs et chercheurs non permanents et assimilés	1
Personnels d'appui non permanents	2
Post-doctorants	0
Doctorants	4
Sous-total personnels non permanents en activité	**7**
Total personnels	**14**

EVALUATION

Overall assessment of the team

The team has pioneered original approaches to delineate the genetic architecture of developmental brain disorders. The attractiveness is excellent as the team experienced fortification through the addition of two permanent researchers and the enrolment of three Ph.D. students. As a young team, they have obtained substantial financial support (around 500 K€) from the ANR JCJC and Inserm, as well as from charities, private companies and internal calls at Imagine. The scientific production achieved during this period has been nothing short of excellent with 35 published articles, including fourteen in highly-reputed generalist journals such as Nature Communications, and eLife. In addition, clinicians affiliated with the group have contributed to 128 collaborative articles, including publications in journals like JAMA and Nature Communications. The outreach of the team is excellent with strong interaction with patient associations.

Strengths and possibilities linked to the context

The Team has established a robust collaboration with clinical departments, providing access to well-defined cohorts of patients with rare genetic diseases. The integration of clinicians within the research group has proven invaluable, offering essential access to clinical information and biological material for constructing unique patient cohorts with Developmental Brain Disorders (DBDs).

The team's complementary expertise has resulted in the identification of 25 new disease-causing genes and the characterisation of genotype/phenotype correlations. Their experimental approaches have led to significant publications in esteemed journals. The team benefits from IHU platforms and technical support, enhancing the quality of their translational research on DBDs.
The team leader was awarded as young principal investigator "JCJC-ANR" 20217-2021 (325K€) and the team received financial support from caritative association for human genetics projects (21k€ + 24k€). In 2021, the lab received a funding from Inserm "Amorçage" (24k€) to exploit single-cell RNA-seq from human cerebellar samples. A new topic on the genetic basis of developmental language disorders was developed and supported by donations from private companies to the lab (130 k€) in 2021. The team received help form Imagine Innogrant and a cross-lab Imagine association.
The team has demonstrated an excellent attractiveness, recruiting four Ph.D. students and establishing scientific collaborations with research groups in Europe and within Imagine. Collaborations focused on modelling brain diseases with human organoids, are expected to be valuable assets in the future. The team has also cultivated strong ties with patient associations, participating in seminars and events, showcasing excellent fundraising ability from national agencies and patient associations like Imagine InnoGrants.
Since the last contract, the team has published 35 articles, including fourteen in international journals such as Nature Communications, eLife, and American Journal of Human Genetics. Clinicians affiliated with the group have contributed to 128 collaborative articles, including publications in journals like JAMA and Nature Communications. The scientific production can be described as excellent.
The outreach is excellent as they maintained strong interaction with physicians and patients' organisations.

Weaknesses and risks linked to the context

The field of DBD research is highly competitive and involves complex molecular physio-pathological mechanisms. To address this, the team should consider recruiting young researchers, including postdoctoral fellows or additional permanent staff scientists, particularly with expertise in bioinformatics.
While funding has been sufficient, the team may need additional sources to sustain an ambitious scientific program. A focus on valorisation strategies could attract additional funding.

Analysis of the team's trajectory

The scientific aims of the team is to gain insights into the pathological mechanisms leading to DBD. For this purpose, they manage to establish links with the departments of Genetics, Neurology, Neuroradiology, Pediatrics and Child Psychiatrics and with several reference centres creating a collection of patients with unsolved neurodevelopmental diseases. A notable strength lies in the complementary approaches adopted by both clinical and fundamental researchers. This collaboration enables the comprehensive characterisation of the phenotypic spectrum resulting from patient mutations, thereby directly benefiting clinical practice. The research projects of the team can be classified in three main topics: human genetic to identify of new genetic defects involved in DBD with direct consequences on patients' molecular diagnosis; basic science to better

understand normal brain development by dissecting disease mechanisms and to develop novel disease models and transfer of knowledge to the diagnostic laboratories to develop improved diagnosis strategies using new sequencing or bioinformatic approaches.

The team beneficiate from access to platforms and core facilities for research including genomics, single-cell, imaging, induced pluripotent stem cells (iPSCs), bioinformatics, and pre-clinical models of Imagine. The team has developed strong national and international scientific collaborations providing expertise in neurobiology, glycobiology, electrophysiology and bioinformatic analyses.

The permanent staff of the team has complementary skills in the fields of clinical genetics, cytogenetics, molecular genetics, cell biology and neurodevelopment. During this term, they obtained a good level of funding and maintained strong interaction with physicians and patients' organisations.
During the last five years, one technician was promoted as IE Inserm, one PI was awarded a professor position (PU-PH) and one PI as a research director position (DR2 Inserm). Additionally, they recruited a CRCN Inserm specialist in neurodevelopmental mechanisms, and a clinician (PH) who is in charge of the national reference centre for congenital cerebellar defects. These changes in the organisation of the team are very positive and validate the team's trajectory.

RECOMMENDATIONS TO THE TEAM

Recruitment of permanent staff members with complementary skills (notably in bioinformatics) will certainly beneficiate to the original and challenging approaches developed by the team to further characterise DBN.
This strategic move will undoubtedly reinforce the team's standing in a highly competitive field, further establishing it as a leader in developmental brain disorder research.

Team 13: Intestinal Immunity

Name of the supervisor: Ms Nadine Cerf-Bensussan

THEMES OF THE TEAM

The team focuses its research efforts on intestinal immunity with two main objectives:1) study of host-microbiota interactions; 2) translational studies of the human gut barrier to study human genetics of infectious diseases.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

"The current focus is appropriate and should be continued. Intestinal immunology and inflammatory bowel disease will be for much longer in the centre of research. The team should continue to aim for publication in top journals."
The team published 31 papers and eleven reviews in the 2017-2022 period. They are published in very high-level journals in the field (Gastroenterology x3, Nat Microbiol x1, Lancet Gastroenterol Hepatol x1, Gut x1, JCI x1, notably).
"The main challenge will be to maintain the focus on clinical problems when the leadership of the team changes. Furthermore, the close cooperation between clinical and basic research will need to be maintained."
"The team should continue its focus on the immune genetics of human intestinal diseases and maintain the link between patients, gene identification and biological studies. The potential of therapeutic applications is promising and it is of utmost importance to follow this track."
This has been achieved by translational studies on the gut barrier, including projects on coeliac diseases, and on monogenic intestinal disorders, with the description of several potentially interesting variants and the implication of clinicians in the team. In addition, close collaborations with the clinics exist and led for example to the development of a targeted NGS panel routinely used in clinical genetics to screen intestinal gene defects.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	2
Maîtres de conférences et assimilés	1
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	5
Sous-total personnels permanents en activité	**11**
Enseignants-chercheurs et chercheurs non permanents et assimilés	1
Personnels d'appui non permanents	2
Post-doctorants	2
Doctorants	2
Sous-total personnels non permanents en activité	**7**
Total personnels	**18**

EVALUATION

Overall assessment of the team

For the 2017-2022 period, the team had an excellent to outstanding publication activity in highly visible journals (Gastroenterology, Nat Microbiol, Lancet Gastroenterol Hepatol, Gut, J Clin Invest), with outstanding fundraising capacity (3.3 M€) and international visibility. The team's non-academic activity was excellent.

Strengths and possibilities linked to the context

Visibility/Attractivness
The team is currently composed of one DR, three CR and two PHU, two PH and two PU-PH (2 PU-PH and 2 CR left the lab during the period). They trained six PhD students, and three post-docs were hired during the period. Five PhD students were authors of one publication, as first author for three of them, and one PhD student was author of six publications, four as first author. Among the three post-docs, only one had a first author research article (out of 2 publications). Therefore, the scientific production in terms of publications for post-doc in particular could have been higher.

The team had an exceptional capacity to obtain grants from national agencies (3 ANR as PI, 1 ARC as PI, 1 plan Cancer, FRM labeled team, 1 INCa-PLBio) for a total of 3 269 k€. It did not appear to have obtained international funding in this period.

The outstanding international visibility of the team was attested by 71 invitations to conferences, with a significant number (22) at international meetings for the team leader, the organisation of three congresses/workshops and editorial responsibilities for the team leader. The team leader also received two international prises (Distinguished Scientific Award, Society for Mucosal Immunology, 2017; Maki celiac disease Tampere Prise, 2018).
Scientific production:
The team had an outstanding scientific production in intestinal immunity, in particular in the study of host-microbiota interactions, with a specialisation in the study of segmented filamentous Bacterium (SFB) by a permanent researcher who left the team in 2020 after obtaining an ERC-consolidator grant. This work was continued by another researcher in the team from 2019. The team also published innovative work in the translational study of the human gut barrier. They demonstrated a hyperactivation of the JAK-STAT pathway in Coeliac disease and sometimes in lymphomagenesis. In addition, they described novel potentially monogenic causes of intestinal disorders, which led to several publications describing new variants, and to the development of a targeted NGS panel for patients. Overall, the team published 20 scientific articles as primary authors, eleven collaborative papers, and thirteen reviews. Many of the papers were published in highly regarded journals (Gastroenterology x3, Nat Microbiol x1, Lancet Gastroenterol Hepatol x1, Gut x1, JCI x1, notably). Overall, the scientific production of the team was excellent to outstanding.

Non-academic activities
The non-academic activities were excellent. The team set up two patient cohorts, and developed two diagnostic tools (one cytometry protocol and one targeted NGS panel) which were transferred to the Necker Hospital. The team participated in interviews with the media (5), interacted with two patient associations, and mentored high school pupils.

Weaknesses and risks linked to the context

Considering the international visibility of the team and the number of staff researchers, the numbers of PhD and post-docs were surprisingly low. The economic and clinical valorisation activity of the work was also quite low. Due to the retirement of the team leader, the team will close in December 2024. This will be a challenge for the other members of the team, some of whom are still in discussions for their future stay.

Analysis of the team's trajectory

Most of the projects will be continued by the different researchers in their future environment, in a logical way. Discussions are ongoing with the future labs.

RECOMMENDATIONS TO THE TEAM

Due to the retirement of the team leader, the remaining team members are encouraged to choose with care their future careers at Imagine or elsewhere.

Team 14: Genetic skin diseases: from disease mechanism to therapy

Name of the supervisor: Mr Alain Hovnanian

THEMES OF THE TEAM

The main focus of the team is on severe genetic skin diseases, including dystrophic epidermolysis bullosa (EB), Netherton syndrome (NS) and Darier disease (DD). They aim at elucidating "molecular mechanisms involved in these diseases by studying patients and developing pre-clinical disease models, identifying factors responsible for their clinical variability and developing new targeted therapeutic strategies". Their studies are based on large cohorts of patients established in the context of national and international collaborations.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

"*There is no specific reply to the recommendations of the previous experts in the self-evaluation report*".
However, it appears that most recommendations were taken into consideration, except for measures allowing to hire a higher number of PhD students and for supporting the Netherton pre-clinical models work by permanent staff.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	4
Maîtres de conférences et assimilés	1
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	3
Sous-total personnels permanents en activité	**9**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	7
Post-doctorants	5
Doctorants	3
Sous-total personnels non permanents en activité	**15**
Total personnels	**24**

EVALUATION

Overall assessment of the team

The report is well structured and clearly written, which is of help for assessment. The team appears to be very strong and highly productive, in both basic science (preclinical models) and clinical research, with excellent integration at the local, national, and international levels.
Attractiveness and scientific production are rated excellent to outstanding and outreach is rated outstanding.

Strengths and possibilities linked to the context

The team leaders evaluate their strengths very well in their self-assessment. The combination of state-of-the-art laboratory work, based on the excellent technical means of the Institute, extensive patient cohorts and data, close links with pharma companies, and the ability to organise or be co-involved in clinical trials is impressively

strong and raises serious hopes that adapted treatments will be developed for patients suffering from congenital skin diseases.

Evaluation area 1: Profile, Resources and Organisation of the Team

The team has a distinctive, internationally recognised scientific profile, which allows impressive scientific progress and translational work. It is clearly aligned with the philosophy and mission of Imagine (genetic identification, pathophysiological mechanisms, treatment). The human resources of the team appear to be adequate. The team has been successful in acquiring numerous competitive and non-competitive grants (2 ANR grants as PI, three additional ANR grants, eighteen grants from Industry and eleven from Foundations and Charities). The technical resources available at the Imagine Institute are plentiful and cover the needs of the team.

Evaluation area 2. Attractiveness

The permanent members appear well integrated in local, national and international organisations and are frequently invited as speakers in scientific conferences; they have established important national and international collaborations and are among the leaders in their field. The team is attractive to young researchers and provides them with adequate training. It also has hosted several international visiting scientists, underscoring its attractiveness.

Evaluation area 3. Scientific production

The team has pursued an impressive number (12) of distinct scientific projects, in most cases up to the stage of publication. The team has produced 103 publications in peer-reviewed journals, conducted or was involved in nine clinical trials and has filed nine patents. Some publications are in top international journals and overall, this level of productivity is well above average, confirming that the overall strategy and mission of Imagine are successful. In detail, team members are first or last author in 56 of the 103 publications, and PhD students/Postdocs are leading authors on twenty publications. The best articles, selected in the portfolio were published in the Journal of Investigative Dermatology, New England Journal of Medicine, and Journal of Allergy and Clinical Immunology. A paper in Lancet in also noteworthy.

Evaluation area 4. Contribution of Research Activities to Society

Team members are in close contact with patient organisations and participated in various actions and events popularising their research.

Weaknesses and risks linked to the context

Weaknesses and risks stem primarily from the closure of the team and the merger with the team1.

Evaluation area 1: Profile, Resources and Organisation of the Team

It is somewhat unexpected, given its profile that the team didn't manage to acquire European funding.
The costs and logistics for maintaining a rather large pre-clinical facility are straining the resources of the team.
Two senior members will reach retirement age during the next phase and it is mentioned at the very end of the self-evaluation report that the team will be integrated in the team 1. No indication is given in the self-evaluation report when this will happen and how the team will be led in the future. Clarification at the site visit was given: the team will be led by a PI hosted by the team 1.

Evaluation area 2: Attractiveness

The team mentions difficulties in finding postdocs for already funded projects. It might be worthwhile to recruit from a larger international basis (Switzerland, Germany, etc).
There is no information in the self-evaluation report about possible promotions or academic advancement of former researchers in the team.

Evaluation area 3. Scientific production

As noticed by the experts of the previous evaluation, it is not clear how research lines are prioritized, especially the projects carried out by a single PhD student or Postdoc.

Evaluation area 4. Contribution of Research Activities to Society

Overall, outreach activities by the team appear rather meagre and their impact might be limited.

Analysis of the team's trajectory

For the coming years, the team names nine projects to be carried out or completed. Five projects are related to ERDB (on-going gene therapy clinical trial, with engraftment of genetically engineered autologous skin in ERDB patients; genome editing strategies for correcting *COL7A1* mutations followed by grafting experiments; splice modulation strategy for *COL7A1*; cell therapy with human MSCs, experimental and clinical; study of Squamous Cell Carcinoma (SCC) developing in RDEB patients. One project each is related to Netherton syndrome (completion of on-going study), to palmo-plantar keratoderma, to acantholytic diseases resulting from impaired calcium homeostasis (already funded by ANR grant), and to Hidradenitis Suppurativa (HS) and associated syndromes. All projects are based on either on-going work or on validated preliminary data and patient cohorts where relevant. They will address disease mechanisms and mainly screen for treatment opportunities using relevant in vitro and in vivo models, as well as clinical work.
These projects are well aligned with the overall strategy of the team and the Imagine Institute. After the merger with the team 1, continuity will be ensured under the direction of one PI from this team.

RECOMMENDATIONS TO THE TEAM

It will be essential to conclude, as far as possible, on-going projects before closure of the laboratory and to speed up the recruitment of the required (and already funded) postdocs via international channels. The initiation of new projects should be planned and coordinated with the team 1.

Team 15: Translational Research for Neurological Disorders

Name of the supervisor: Edor KABASHI — Mr Edor Kabashi

THEMES OF THE TEAM

The team is dedicated to unravelling the pathophysiological features of Amyotrophic Lateral Sclerosis/frontotemporal dementia, Developmental Epileptic Encephalopathies (DEE) and related neurological disorders.
The team has developed an integrated genetic modelling of diseases and new clinical trial methodology for accelerated drug discovery. The team has innovatively developed cellular models, including neuronal cultures derived from induced pluripotent stem cells (iPSC) and genetic models in zebrafish to pinpoint shared pathogenic pathways that can be targeted pharmacologically.
To advance the field, the team has put forth sophisticated computational tools designed to define biomarkers, contributing to improved classification of DEEs patients, with the creation of a newly developed platform that combines multielectrode arrays and patch clamping techniques within the Necker campus. This initiative show their commitment to cutting-edge methodologies and collaborative efforts.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

"The previous committee's recommendations to enhance interaction with clinicians within the IMAGINE framework and increase the team's workforce have been duly addressed".
Since the last evaluation, the overall team size has more than doubled, with a notable increase in the number of clinicians actively engaged in research projects. These intensified collaborations between fundamental and clinical research have resulted in meaningful modifications to clinical practices for Amyotrophic Lateral Sclerosis (ALS) and Developmental and Epileptic Encephalopathies (DEEs).

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	1
Maîtres de conférences et assimilés	1
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	0
Sous-total personnels permanents en activité	**4**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	5
Post-doctorants	5
Doctorants	5
Sous-total personnels non permanents en activité	**15**
Total personnels	**19**

EVALUATION

Overall assessment of the team

The attractiveness of the team is rated as outstanding because of the international reputation of both leader PIs of the team. The PIs are involved in national and international clinical networks, international conferences organisation and honoured several invitations at national and international congresses. The team attracted a high number of PhD (5) and post-docs (3) and got important fundings at both European (1 ERC consolidator, 1 ERC POC, 2 FP7 grants…) and national (5 ANR, AFM, FRM grants….) levels. The scientific production is qualified as excellent to outstanding. The team has published papers in leading journals during this period, including articles in the Journal Clinical investigation, New England Journal of Medicine, Nature Communication, Jama Neurology. In summary, more than 200 publications have been produced during the last 5 years. The outreach activity of the team is outstanding (ongoing contracts with star-ups, pharma partners for ongoing clinical trial, participation to scientific boards of patient association).

Strengths and possibilities linked to the context

The team is aiming at accelerating translational studies on pathogenic mechanism in amyotrophic lateral sclerosis (ALS) and translational features of developmental and epileptic encephalopathies (DEEs) and related disorders. For this purpose, they build up a research group that gather together clinicians and fundamental researchers that led to an outstanding visibility and recognition. In the past years, they managed to recruited impressive number of PhD students (5) and postdocs (3). They also develop collaborations with important research groups at the national and international levels.

The team has obtained important funding at both European level (1 ERC consolidator and 1 ERC proof of concept, 1 EU twinning program, 1 EJP-RD funding and 2 FP7 grants) and national level (5 ANR financed projects, funding from FAMA and KCNB1 Foundations and industry partnership). These multiple funding validated the global scientific strategy of the team.

The international visibility of the team is validated by many invited presentations in scientific meetings and by the participation of the team's member to the scientific boards of patient association. Two PIs participate at the board meeting for rare epilepsies of Roche Foundation and scientific board meetings of other pharma companies. The team has submitted patents for genome editing in ALS, with focus on the major genetic cause.

The team has an excellent to outstanding scientific production both in scientific and clinical journals in which they are aiming at deciphering the genetic and molecular mechanisms of ALS and DEEs. The team has published papers in leading journals during this period, including articles in the *Journal Clinical investigation, New England Journal of Medicine, Nature Communication, Jama Neurology*. In summary, more than 200 publications have been produced during the last 5 years. Publications as recommended in the ERC and ANR guidelines are submitted as open access for scientific transparency and to render digital most of their research findings.

The translational potential of the team's work is validated by ongoing contracts with the French start-up, Inflectis and the Swiss start-up, Vandria to test compounds in ALS models and by collaboration with pharma partners for ongoing clinical trials in DEEs. The team is also developing collaborations with important pharmaceutical companies for genetic therapy and repurposing molecules for epileptic disorders as well as ongoing collaboration with a start-up developing wearables for measuring EEG activity. The outreach activity of the team is outstanding.

Weaknesses and risks linked to the context

The team moved in 2018 from the Institut du Cerveau et de la Moelle épinière to Imagine. They experienced administrative hurdles making difficult personnel hiring, grant administration and resource planning. If the recent recruitment of Ph.D students indicates that these hurdles are over, the ratio between permanent staff and the non-permanent staff may represent an obstacle to insure the burden of important Ph.D students training.

Analysis of the team's trajectory

The team has grown substantially from one to four PIs. The permanent staff of the team is now composed of two tenured Inserm researchers and two clinical researchers. In 2022, Imagine created a CDI position for a lab manager. This increased number of scientists was necessary to sustain the diversity of the research themes

developed by the team. To maintain this dynamic, the team will support the candidature of two senior postdocs (Drs. de Calbiac and Raas) for researcher positions at Inserm in 2024. Two clinical researchers will join the team in a near future and they are training three young clinicians to enter in a MD/PhD program in 2023.
The team is beneficiating of the in-house platforms at the Necker campus, including proteomics, genomics, metabolomics, cell sorting, iPSCs, imaging platforms and pre-clinical models facilities at Imagine. The team is involved in the coordination of these platforms and in the processes leading to acquisition of new common equipment.
At the national and international level, the team is involved in collaborations for patient repositories and continued his participation to advanced multicentric clinical trials. One of the strengths of the team lies in the interaction between clinical and fundamental researchers. This collaboration enables the comprehensive characterisation of the phenotypic spectrum resulting from patient mutations, thereby directly benefiting clinical practice.

RECOMMENDATIONS TO THE TEAM

The team has made substantial progress in aligning with the objectives set in the previous evaluation. Their noteworthy success in securing grants at both the European and national levels, coupled with the impactful translational research approaches, serves as validation for the scientific strategy devised by the research team. Looking ahead, the team faces the challenge of sustaining its growth trajectory and maintaining an excellent research standard. To meet this challenge, a strategic imperative is to augment the permanent staff by actively recruiting young researchers. This proactive step is crucial to ensuring the team's continued success and its ability to contribute significantly to the field of ALS and DEE.

Team 16: Lymphocyte activation and susceptibility to EBV

Name of the supervisor: Mr Sylvain Latour

THEMES OF THE TEAM

Team 16 studies genetic predisposition to infectious diseases, with a focus on Epstein Barr Virus (EBV) and related pathologies. The team works in the field of In-born Errors of Immunity, using cohorts of patients and pre-clinical models to investigate the genetic origins of these pathologies. They put much effort into the translation of their discoveries into clinical applications.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

An opportunity for the team would be to apply its expertise towards the unravelling of EBV-associated diseases like Burkitt's lymphoma and nasopharyngeal carcinomas which remain worldwide health issues.
The PI participated to investigations on Burkitt's lymphoma (2 publications).

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	1
Maîtres de conférences et assimilés	1
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	1
Sous-total personnels permanents en activité	**6**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	1
Post-doctorants	1
Doctorants	5
Sous-total personnels non permanents en activité	**7**
Total personnels	**13**

EVALUATION

Overall assessment of the team

Team 16 is composed of five senior scientists, including physicians and researchers. It has also been highly successful obtaining grants, primarily from charities and French national agencies, further showing its excellent to outstanding attractiveness. The scientific production is excellent to outstanding, with numerous original articles in top-range journals, both as leader authors and collaborators. The outreach of the team is excellent, as demonstrated by partnerships with a biotech, two CROs and the transfer of a test to clinical practice.

Strengths and possibilities linked to the context

The international reputation of the team is attested by invitations to international meetings (19), for seminars and collaborations with local, national and international teams. They were attractive for PhD students and postdocs (1 French and 3 Japanese), who obtained competitive grants. One of the postdocs was recruited as CR at Inserm and has remained in the team since, and two senior scientists will join the team in 2025. The team is part

of four consortiums related to medical or technical issues. The researchers taught in various Masters of different universities, the PI is codirector of a doctoral school in Paris Cité University and one of the researchers is part of an international immunological society. Taken together, they strongly contribute to the construction of the European research area.
The team obtained a large number of national grants (5 from ANR or INCa, 3 from charities or founding for innovation), as well as grants from two consortia, INCa Pediac and COVIRIC. They spent 2,926 k€ in 6 years (488 k€/y), which is a very high level of funding for a team of this size.
The team has an outstanding publication level with fifteen original articles in top-range journals as leader authors (Sci Immunol (1), J Exp Med (4), J Clin Invest (2), J Allergy Clin Immunol (2), EMBO Mol Med (1), J Clin Immunol (1)), and 28 as collaborators (Science (1), J Exp Med (3), Sci Immunol (1), Annals of Rheum Dis (1), Nat Comm (1), Gastroenterology (1), J Allergy Clin Immunol (1), Eur J Immunol (3)).
The innovative activities of the team is remarkable. They published two patents, on the pharmaceutical inhibition of T-cell proliferation and of EBV-driven proliferative diseases. They had partnership contracts with a Biotech, Step-Pharma created by the PI in 2014, and two CROs, Sygnature and Kurma, for the development of chemicals inhibiting lymphocyte proliferation, now in clinical trials. They developed a diagnostic test for EBV diseases and provided a proof-of-concept for the use of gene therapy in lymphoma.

Weaknesses and risks linked to the context

Two out of three past PhD students spent more than 3 years in the lab, which is beyond the three recommended years.

The report lacks a description of vulgarisation/interaction with the general public. This could be a missed opportunity to highlight their success and build/reinforce public support for research.

Analysis of the team's trajectory

The team will develop research activities in line with their previous results, but also new investigations, notably B-cell defects, with the arrival in 2025 of two permanent scientists, a CNRS DR and a MCU-PH. Altogether, seven research axes are defined by the team for the next contracts, which seems highly ambitious.

RECOMMENDATIONS TO THE TEAM

The main recommendation of the committee to the team is to pursue their excellent production in basic research and their translational activity. In addition, opportunities for public outreach are encouraged to be considered and sought.
We also recommend to supervise closer the PhD students, so that they could contribute better to the scientific production, and in less time.

Team 17: Heart Morphogenesis

Name of the supervisor: Ms Sigolène Meilhac

THEMES OF THE TEAM

The team focuses on developmental biology and cardiovascular morphogenesis, with the goal of unravelling the embryological mechanisms shaping the heart and understanding their implications for human diseases. Employing an interdisciplinary approach, the team integrates data from patients with congenital heart defects and pre-clinical models imaging, utilising advanced omics, microscopy, and cutting-edge computational science. This comprehensive strategy enables them to uncover novel molecular and cellular dynamics within the context of developing three-dimensional organs.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

"The previous recommendations from Hcéres underscored the necessity to elevate scientific output, recruit new Principal Investigators (PI), and cultivate collaborations with teams within Imagine that share common scientific interests".
All these recommendations have been successfully implemented.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	2
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	3
Sous-total personnels permanents en activité	**7**
Enseignants-chercheurs et chercheurs non permanents et assimilés	1
Personnels d'appui non permanents	1
Post-doctorants	2
Doctorants	2
Sous-total personnels non permanents en activité	**6**
Total personnels	**13**

EVALUATION

Overall assessment of the team

During the 2017-2022 period, the team significantly enhanced its national and international visibility through ground-breaking research which allows to qualify the attractiveness as outstanding. They secured substantial funding, with 2.5 million € as a coordinator and over 26 million euros as a partner in multiple projects. Additionally, the team's attractiveness enabled the recruitment of a high-profile researcher (CRCN) since 2022. Key indicators of their success include the publication of excellent to outstanding original and review articles in excellent journals such as Nat Comm and Nature Reviews Cardiology. The team non-academic activities are excellent.

Strengths and possibilities linked to the context

The team's manifests outstanding national and international recognition illustrated by numerous invitations to contribute to reviews (7) and scientific seminars (47) and has chaired two international meetings. Collaborations levels are prominent, fostering interdisciplinary initiatives. The team has actively initiated and coordinates two networks in cardiology and developmental anomalies, promoting multidisciplinary interactions.

The team's dedication to scientific excellence is evident through awards and recognitions, including a L'Oréal award and the Pasteur Valery Radot Prise. The team leader's promotion further underscores her globally recognised leadership. Active involvement in scientific societies, committees, and editorial boards contributes to advancing the scientific community.

The team has excelled in securing funding. As the grant coordinator, she raised 2.5M€, with fellowships totalling 1M€. Funding sources encompass national and international agencies, as well as charitable organisations.
Playing a pivotal role in training seven PhD students and five post-docs, the team contributes significantly to knowledge transfer. Engaging in teaching activities in France and abroad highlights their commitment to education. Participation in thesis committees, juries, and mentoring MD students further emphasises their impact on knowledge dissemination.

The team has demonstrated excellent to outstanding productivity, excelling in diverse areas, from pioneering modelling techniques to significant breakthroughs in heart development. Their research findings have been disseminated through publications in leading journals and top specialty publications. With over 33 articles, three book chapters, and an extensive list of more than 100 communications and 57 posters presented both nationally and internationally. Their work advances scientific understanding, providing innovative frameworks for studying heart morphogenesis. Notable findings include quantitative 3D Imaging and Modelling, identifying a novel buckling mechanism in heart looping, unveiling the transient role of Nodal during heart looping, and discovering the critical role of Greb1l in criss-cross heart. The filing of an international patent emphasises the economic implications of their research, especially in advancing treatments for cardiac diseases using Hippo pathway modulators.
The team *Non-academic activities* are excellent. It excels in effective communication and outreach across various audiences. Engaging scholars, media, patients, and artists, they disseminate research outcomes through press releases, social media, and newsletters. Their commitment to public understanding is evident in class tours at Institut Imagine. Collaborations with artists and photographers produced impactful representations of embryonic hearts. The team actively interacts with patients, conducting seminars, workshops, and contributing to patient forums and educational events, ensuring that research benefits directly reach the intended audience.

Weaknesses and risks linked to the context

Visibility/Attractiveness
The team is actively pursuing numerous ground-breaking research projects in an intensely competitive field. The team leader has successfully recruited a highly skilled full-time researcher, underscoring the ability to attract top talent. However, it is equally important for the leader to prioritize the turnover of non-permanent staff to maintain a dynamic and diverse research environment.

Scientific production
There are no significant weaknesses identified.
Non-academic activities
No major weaknesses identified.

Analysis of the team's trajectory

In the upcoming contract, the team is well-positioned to build upon their strong scientific foundation and capitalise on ongoing research initiatives, leveraging the expertise of newly permanent researcher. The focus remains on addressing novel challenges in heart morphogenesis to enhance the understanding of complex congenital heart defects.

Despite the competitive nature of heart morphogenesis research, the team's integrated model stands out for its originality and promising potential. The overall project is deemed robust, acknowledging the inherent challenges associated with the complexity of heart morphogenesis and related diseases.

Trajectory key points:

The team has secured substantial funding exceeding 1.5 million euros until 2025 from various sources, including ANR, SVRF, AXA, Equipe FRM, and Revive Labex. Ambitious plans include seeking additional major funding through an ERC Advanced grant and ANR jcjc, highlighting a commitment to sustained financial support.
The team further intends to collaborate extensively with interdisciplinary national and international networks, tapping into the expertise of state-of-the-art core facilities within Imagine and engaging with associated partners.
Solid interactions with clinicians on the Necker campus reinforce the project's success, ensuring a translational approach and aligning with clinical needs.

Overall, the proposed projects align seamlessly with the broader strategy of both the team and the Imagine Institute, reinforcing the relevance and impact of their work.
In conclusion, the team is poised for continued success, supported by robust funding, collaborative initiatives, and a strategic alignment with the Imagine Institute's overarching goals. Their commitment to advancing knowledge in heart morphogenesis reflects a comprehensive and forward-looking approach.

RECOMMENDATIONS TO THE TEAM

The team has expanded its size, and considering the multitude of projects, it is crucial to persist in the strategy of recruiting fresh talent, including researchers and engineering staff.

Team 18: Genome Dynamics in the Immune System

Name of the supervisor: Mr Patrick Revy & Mr Jean-Pierre De Villartay

THEMES OF THE TEAM

The team "Genome Dynamics in the Immune System" focuses its research projects to explore the causes and consequences of genomic instability that may be associated with Mendelian diseases affecting the hematopoietic system, programmed genetic recombination processes (e.g. V(D)J recombination), and chromosomal translocations associated with cancers.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team should publish even higher impact papers, (...) new relationships between bone narrow failure, DNA repair defects, and telomere biology;
The team published several articles and reviews in high ranked international journals including Mol. Cancer, J.Exp. Med, Mol. Cell, Nat. Commun, Blood (2), ELife, Cancer Res, JACI, Cell Rep, Nat. Rev. Genet. (2), EMBO Mol Med.

Transfer of this basic knowledge to more applied translational research is encouraged;
They set up a collaboration (Cifre) with Genomic Vision as well as a collaborative work with Traverse Biotech (US biotech) to develop therapeutic approach in ALCL lymphoma. They also recently identified and patented potential new therapeutic targets for anti-cancer treatment (demand of International Patent 2021).

(..) promote synergies between the activities of the four staff scientists. Increasing the international visibility of one of the two PIs, whose scientific activity is excellent;
Numerous publications were done with at least two of the three researchers (J allergy Clin Immunol 2019), or even some with all three (Blood 2022, Nature Commun 2021, 22, J allergy Clin Immunol 2021…).
The PI arrived in 2016 remains singular in the team and synergy is still not optimal.

pursue the research program, nurturing close interactions with clinicians and establishing collaborations with DNA repair and telomere groups
The quality of publications in this field attests to the success of research projects carried out in this area.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	1
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	3
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	3
Sous-total personnels permanents en activité	**6**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	3
Post-doctorants	0
Doctorants	6
Sous-total personnels non permanents en activité	**9**
Total personnels	**15**

EVALUATION

Overall assessment of the team

The team has an excellent scientific production with 72 publications in international journals (Blood 2019, EMBO Mol Med 2019, Nature Commun 2021, ELife 2021). The attractivity and visibility are also excellent within fund raising from national (ANR, INCA PLBIO) and caritative sources (AT Europe, LNCC, CEREDIH…). The PIs also participate in the scientific committees (ARC, Ligue …) as well as in scientific networks (React4kids). Finally, the team has excellent outreach and non-academic activities with one patent (2021) and two collaborative contracts (Genome Vision-Cifre, Traverse Biotech).

Strengths and possibilities linked to the context

- The main strength of DGSI resides in its long-term close association with a clinical department (UIHR, Dir. Pierre Quartier, Paris, France) specialised in the study of very rare Mendelian diseases including inherited bone marrow failures syndromes (IBMFS) and primary immunodeficiency (PID). One PI provides a critical link with this department as well as with other national and international clinicians working on these rare diseases.

- Publications of the DGSI lab members allow them to be recognised in their fields internationally and to obtain regular funding, to get numerous grants for PhD students and to be labelled by the Ligue contre le Cancer.

Weaknesses and risks linked to the context

- One important weakness is the absence of a critical mass of permanent technical staff to assist with the day-by-day analysis of patients' samples. This staff is currently recruited temporarily from their grants.

- One PI is an expert in genome editing approaches but for the time being, these skills seem not be sufficiently exploited and/or promoted.

- The team had only 1 post-doc during the evaluation period. This might reflect a lack of attractiveness for foreign and valuable post-docs, in particular.

Analysis of the team's trajectory

The research projects developed within the team have the common objective of determining the causes and consequences of genetic alterations, both germline and somatic, responsible for cellular stress and genomic instability and associated with primary immunodeficiency (PID), inherited bone marrow failure syndrome (IBMFS) as well as oncogenic initiation and evolution.
The projects of the team have evolved and are now no longer specifically focused on the genome in the immune system but more broadly on the dynamics of the genome in human pathologies. The future team will be renamed "Genome Dynamics in Human Diseases" to better reflect the thematic evolutions.
The projects of the team will associate patient-driven analyses to the development of more basic science-driven approaches through the design/study of innovative cellular and pre-clinical models and state-of-the art technologies dedicated to monitor genome stability and modifications (Genome editing, ChIP seq, replication timing, and molecular combing).

RECOMMENDATIONS TO THE TEAM

- Due to its excellence level, the team could target international grants to improve the visibility and attractiveness.

- The team could improve and reinforce the link between the four PIs and specially to include the genome editing expertise of one PIs in future projects.

- The team could improve the valorisation of the research results and develop more collaborations with non-academic industrial partnerships.

Team 19: Neurogenetics and neuroinflammation

Name of the supervisor: Mr Yanick Crow

THEMES OF THE TEAM

The themes of the team are to define the clinical, molecular and pathological characteristics of novel type I interferonopathies. More precisely, the team aims at defining novel genes/proteins and cellular processes which, when disrupted, lead to innate immune system, including the role of mitochondrial nucleic acid to trigger interferon signalling, the role of innate immune system activation in interferon-mediated lung inflammation, the contribution of inborn errors of the type I interferon pathway to psoriasis and psoriatic arthritis, and the investigation of the link between ATRX and innate immune signalling.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

"The main concern of the previous committee was about the fact that the team leader, Yannick Crow had obtained a position at the University of Edinburgh in 2028 at the same time continuing to direct the Laboratory of Neurogenetics and Neuroinflammation in Imagine".

This recommendation has been considered. The two teams have highly complementary skills - with a clinical immunology orientation in Paris, and a more 'functional' emphasis of the programme in Edinburgh. Yannick Crow is visiting each month the Paris lab and joint meetings as well as video meetings are held by video each week.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	1
Maîtres de conférences et assimilés	1
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	2
Sous-total personnels permanents en activité	**5**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	0
Post-doctorants	0
Doctorants	2
Sous-total personnels non permanents en activité	**2**
Total personnels	**7**

EVALUATION

Overall assessment of the team

The team is a leader in the field of interferonopathy and related disorders and is evaluated as outstanding or excellent to outstanding in all domains. The team was strengthened by recruitments and now includes two full-time researchers, two post-docs and two PhD students. The scientific production is outstanding, with publications in leading journals. The research projects are cutting edge and there is a potential for translational applications. The complementary skills of the two teams will be useful to address the scientific questions.

Strengths and possibilities linked to the context

The team has an outstanding visibility and recognition and is attractive for students and postdocs. There are two full-time tenured researchers in addition to the PI. Two PhD students have joined the team during this contract (1st and 2nd year of PhD, respectively). The two senior post-docs in the lab obtained permanent positions to strengthen the team: one was awarded a Marie-Curie Fellowship in 2020, becoming Chargé de Recherche in 2022; while the other one was appointed MCU-PH in 2020, and obtained her HDR in 2021.

The team has obtained grants from national agencies (2 ANR as PI, 3 ANR as co-PI) as well as from the European Community (1 ERC).

The international visibility of the team is attested by many invited presentations (mainly done by the team leader but also by another PI of the team).

The team has an outstanding scientific production with a long-lasting experience in deciphering the genetic and molecular mechanisms of the interferonopathies. The team has published four major papers in leading journals during this period, including two articles in the Journal of Experimental Medicine (J Exp Med, 2020; J Exp Med, 2021), one in the New-England Journal of Medicine (N Engl J Med, 2018) and one in Nature Genetics (Nat Genet, 2020). Globally, 205 publications have been produced over the last period.

There is a high and unique translational potential of the team's work. A first experience was the use of JAK1 inhibition in Aicardi-Goutière syndrome.

The outreach is excellent to outstanding, with dissemination of results to the local clinicians, affected patients and their families and to the general public through the Open Days.

Weaknesses and risks linked to the context

There is not major weakness. As for the last term, the fact that the PI is leading two teams, in Paris and in Edinburgh, may be challenging.

Analysis of the team's trajectory

During the next contract, the group of one PU-PH from the team 14 will be assimilating in the laboratory, and brings complementary interest. The overall program of the team will be to continue to define the cellular contexts in which self-derived nucleic acid ligands are generated and sense, and to continue to try to block the generation of self-derived nucleic acid or the downstream interferon stimulus in the effort of translation into clinic.
There are six complementary work-packages with secured funding: WP1: Clinical, molecular and pathological definition of further novel type I interferonopathies, WP2: Mitochondria and innate immune system activation (One recently acquired ANR (JCJC) funding appointed as a PhD candidate), WP3: Exploration of interferon-mediated lung inflammation, WP4: Investigation of the contribution of inborn errors of the type I interferon pathway to psoriasis and psoriatic arthritis, WP5: Investigation of the link between ATRX and innate immune signalling, and WP6. Clinical translation nationwide French multidisciplinary clinic, initiated by one PI.

RECOMMENDATIONS TO THE TEAM

There is not major recommendation.

Team 20: Inflammatory Responses and Transcriptomic Networks in diseases

Name of the supervisor: Mr Mickaël Ménager

THEMES OF THE TEAM

Team 20 main topic is to study the inflammatory Responses and Transcriptomic Networks in diseases aiming at 2 different axes of research: the relationships between HIV and the innate immunity and a methodology development on Single-cell multi-OMICs approaches.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

None, the team was created in 2017.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	3
Sous-total personnels permanents en activité	**4**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	2
Post-doctorants	2
Doctorants	1
Sous-total personnels non permanents en activité	**5**
Total personnels	**9**

EVALUATION

Overall assessment of the team

The team has an excellent scientific production with four main publications (out of 16) in excellent international journals (as Cell Report, 2022). The attractivity and visibility are excellent to outstanding with around 7 Millions Euros in Fund raising (ATIP, ANR, SESAME) illustrated by the group leader being the PI of one of the Workpackage of the RHU Attraction, and the founder of the Singlecell@imagine platform. Finally, the team has excellent Outreach and non-academic activities with two patents (2020,2021) and four private collaborative contracts (such as Sanofi, 10X) and media appearances.

Strengths and possibilities linked to the context

The scientific production of the team is excellent with 16 publications and four as main author (Cell report 2020, FCIMB 2021, MED 2021, JACI 2023) and several collaborations due to the single cell omic approaches.
The visibility and attractiveness of the team is excellent to outstanding for a young team that has established both a platform and research activities within the last period. the team succeeded in establishing interesting areas of studies in the field of inflammatory responses, at the same time as being able to setup the single-cell multi-OMICs technologies at Imagine Institute. Several funding coming from different sources as PI (1 ATIP Avenir

2017, 1 ANR 2021, 1 Cifre 2020 and 1 emergence ville de Paris 2018) and also as coPI (1 FRM 2019, 1 INCA 2020, 3 ANRs 2021 and 2022) were secured, allowing the recruitment of two postdocs, ten engineers and computational biologists (1 with a permanent imagine position), two PhD students (both completed with 1 first author and co-first author publications MED 2021 and in revision), all embedded in the same team, to reach an average size of ten people. A SESAMe grant was obtained to buy equipment for the single cell platform (2020). Finally, the PI obtained 1 price (Delheim college de France 2020).
The outreach and non-academic activities of the team are excellent with two patents (on myocardis and HIV), several partnerships with private companies (Sanofi, Adlin Sciences and Gencovery) and several efforts to share knowledge with the grand public (FAIR events 2021 and 2022, Fetes de la sciences, and media appearances France2, Europe1).

Weaknesses and risks linked to the context

The only weakness identified for the team is the time and resources injected for the development of the singlecell@imagine platform without a critical mass of permanent staff. Despite being successfull the lack of long-term secured expertise could lead to slowing down the research activities of the PI and the team. The scientific impact of the publications should also be prioritized in order to improve the competitivity of the postdocs to obtain permanent positions and attract additional high-level profiles.

Analysis of the team's trajectory

In term of structuration and governance, the trajectory of the team relies on:
mostly focusing its main research activities on the exploration of autoimmune/autoinflammatory diseases through single-cell multi-OMICs combined with state-of-the-art machine-learning (A.I) based algorithms.
-orienting towards more complex multifactorial diseases like juvenile Idiopathic arthritis (JIA) and Systemic lupus erythematosus (SLE) (in collaboration)
-developing tools and methods based on functional and diseases-related molecular signatures coupled with machine-learning algorithms to generate, in a systemic manner, a single-cell multi-OMICs Atlas of children at Necker's hospital and clusterise patients at the molecular level.

In term of Organisation and life, the team will build on its previous experience and will try to keep the same type of organisation regarding human resources. The PI will look forward to obtain an Inserm permanent position for a postdoc of his team (one candidate identified). Imagine Institute will provide wto permanent positions, in order to secure computational biologists with valuable skills in single-cell analyses (one candidate on 2 identified).

RECOMMENDATIONS TO THE TEAM

One of the risk identified is the lack of critical mass to ensure both a competitive research activity and a rapid and constant growth of the single cell platform with rapid expansion of users and demand on specific and various expertise associated with. We recommend to the team to rapidly attract a permanent scientific leader for its research activity but also in the meanwhile recruit a leader as manager of the platform to leave the PI focusing on specific developments (AI) and research projects.

Team 21: Chromatin and Gene Regulation during Development

Name of the supervisor: Ms Annarita Miccio

THEMES OF THE TEAM

The Laboratory of Chromatin and Gene Regulation during Development main research interests are the transcriptional control of haematopoiesis, and the development of therapeutic approaches to hematologic genetic disorders,(β-hemoglobinopathy). The team has a scientific expertise in epigenetics, regulation of gene expression, LV technology for the genetic modification of HSCs, haematology and gene therapy.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

A – The team has shown that it was capable of publishing and training the next generation of scientists, it should now try to reach the next tier of journals.
33 publications in five years are a clear response to this recommendation with high impact publications (Blood, Nat com).

B – *The team should continue to take advantage of the great mentoring possibilities offered at IMAGINE regarding hematopoiesis and gene therapy. The opportunity to have insights from Ms Marina Cavazzana, Ms Isabelle André-Schmutz and Mr Alain Fisher is priceless for a young team.*
With 32 grants and an ERC consolidator, the PI has found her own path.

C – the goals of the team are extremely ambitious it should establish clear fall-back strategies if some of the aims are not reached.
For the moment all aims have been achieved.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	5
Sous-total personnels permanents en activité	**6**
Enseignants-chercheurs et chercheurs non permanents et assimilés	2
Personnels d'appui non permanents	3
Post-doctorants	1
Doctorants	4
Sous-total personnels non permanents en activité	**10**
Total personnels	**16**

EVALUATION

Overall assessment of the team

The team is outstanding in many directions with a scientific production in the highest journals and 33 publications (including 25 main authors as Blood and Nat com 2022 and 14 reviews), visibility and attractivity with an expanding group (including 4 postdocs and 3 PhDs), 73 oral communications in conferences (including ASGCT) and an outstanding found raising capacity with 24 grants (ERCcog, 2 EU-Horizon with one as PI). Outreach and non-academic activities are outstanding with thirteen patents, five private collaborative contracts (incl Sanofi, astrazeneca, cellectis), three clinical trials ongoing, and a very active dissemination of their research data to the public and the patients.

Strengths and possibilities linked to the context

The team has an outstanding internationally recognised scientific production with 33 publications in excellent journals (14 reviews and 25 as main author). In particular it is worth to cite 3 axes on publications:
-transcriptional regulation in normal and diseased hematopoietic stem cells (HSCs) and their progeny with excellent publications (Romano, iScience, 2020; Lagresle, Haematologica, 2018) with follow up using of patients (Magrin, Nat. Med 2022).
-development of genetic engineering tools in clinics for Sickle cell disease-SCD (Weber, Mol Ther Methods Clin Dev, 2018; Ramadier, Mol Ther, 2022).
-Studies on globin gene regulation to develop CRISPR/Cas9 strategies for these diseases (Antoniani, Blood, 2018; Lattanzi, Mol Ther 2019, Weber, Sci Adv, 2020; Antoniou, Nat Comm, 2022; Hardouin, Blood, 2022).
The attractivity and visibility of the team is outstanding. Over the recent years, the team has been internationally recognised in the field of gene therapy with 73 conference proceedings (several invitations in the American Society of Gene Therapy). Furthermore, they have attracted international scientists, obtained international, national and local grants and acquired renowned technological skills (24 grants and 16 fellowships in total) with one DIM grant (2018, 2022), two AFM research grants (2019, 2022), four ANR PRCI (1 as PI 2022), and 3 European grants (1 ERC Consolidator grant 2020, and two collaborative grants Horizon-Research and Innovation Actions and Horizon-Pathfinder), collecting almost 6 million euros in the period.
Outreach and non-academic activities are outstanding. The team filed thirteen patents and six invention declarations since 2017 (none licensed yet). The PI has been consultant of several biotech companies in the field of gene therapy and is envisaging to create her own biotech. Several partnerships and collaborations with biotech companies have been established (Cellectis 2020, Sanofi award 2019), The team is very active in dissemination to the public, the patients (Bourse de diffusion for a PhD of the team) the PI is member of the ARRIGE association.

Weaknesses and risks linked to the context

The team does not present any weakness but one risk is a "growth crisis" upon the rapid development of the team. A project manager is associated with the activity of the team but might necessitate a permanent position to secure and follow all the ongoing projects.

Analysis of the team's trajectory

The team will organise its activity around three axes:

-Project 1 to bring to the clinic the newly developed LV-based gene addition strategies for β-hemoglobinopathies and other hematopoietic disorders
-Project 2 to use novel, cutting-edge genome editing technologies to develop gene therapy approaches for β-hemoglobinopathies and other hematopoietic (and non-hematopoietic) disorders
-Project 3 to investigate the mechanisms underlying the pathophysiology of β-hemoglobinopathies and other inflammatory hematopoietic disorders (in HSCs and their committed progeny) to ameliorate gene therapy strategies.
To reach these goals, the team is expecting to welcome in 2025 E. Six, who is leading a small subgroup at Imagine already. Six's expertise relies on the exploration of human hematopoietic stem and progenitor cell in the context of gene therapy trials.

In term of funding the team has a long-term visibility at the scale of research, up to 2027 with a variety of funding and research networks as illustrated by the EDISCD consortium and others, supported by Horizon-Pathfinder

grants, ANR-PRC grants, and AFM research grants, continuing partnerships with biotech/pharma companies (SmartImmune, Butantan, AstraZeneca, Cellectis and Algentech).

RECOMMENDATIONS TO THE TEAM

The team has an outstanding progression but would have to take care of the theme leaders and project managers within the team to guarantee a long term stability and follow up to all the projects.

Team 22: The Clinical Bioinformatics laboratory

Name of the supervisor: Mr Antonio Rausell

THEMES OF THE TEAM

Team 22 develops computational approaches (statistical methods, machine learning algorithms, bioinformatics pipelines) and network architectures (cloud/edge computing, federated learning) for clinical applications, particularly in patients with rare genetic diseases. They focus on two main themes: interpretation of rare germline genetic variants and single cell functional genomics data analysis. They integrate broad molecular phenotyping with deep clinical records analysis (e.g. EHR) as well. A strong emphasis is placed on building infrastructure such that their analyses are returned to clinicians and inform clinical care.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

"The unique potential weakness might stem from the potential isolation of team 20 within the Institute. Of note team 20 has established multiple connections with other laboratories of the Ile de France region that are interested in similar topics de facto counteracting this possible weakness".
The team is now well integrated within Institut Imagine contributing to multiple internal collaborations and large RHU projects. Notably it now includes three additional senior permanent researchers in the team (N GARCELON, A BURGUN, and P CHASTE), each with their own expertise and network of collaborators.

"We would recommend monitoring precisely the growth pace of the team in order to avoid possible management pitfalls".
No problems are identified in the growth pace of the team and no management pitfalls are apparent.

"The committee recommends to carefully match resources with projects and requests for collaboration to avoid overstretching the team forces".
The team, which had been initially formed shortly before the previous Hcéres, has done an excellent job of maintaining focus and not becoming over-dispersed or turning into a type of bioinformatics core service. The team's research includes both "methods" based projects where they develop new algorithms and computational technologies as well as collaborative, applied research in specific genetic diseases where the scientific/biomedical questions dovetail with their particular computational strengths.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	1
Maîtres de conférences et assimilés	1
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	1
Sous-total personnels permanents en activité	**3**
Enseignants-chercheurs et chercheurs non permanents et assimilés	1
Personnels d'appui non permanents	1
Post-doctorants	1
Doctorants	3
Sous-total personnels non permanents en activité	**6**
Total personnels	**9**

EVALUATION

Overall assessment of the team

The attractiveness of Team 22 is excellent to outstanding with three senior personnel and a significant numbers of trainees and visiting researchers from both France and international. The team has also been highly successful obtaining funding both as coordinators and collaborators on multiple grants. The scientific production of the team is excellent to outstanding, both in terms of publications and software tools for the community. The outreach of the team is outstanding, particularly in educational leadership and diagnostic services.

Strengths and possibilities linked to the context

The team has an strong national and international reputation, attested to by invited seminars at leading conferences (American Society of Human Genetics, International Society of Computational Biology, European Conference on Computational Biology) and institutions (Yale School of Medicine, University of Kent). The lab includes three senior personnel, a total of six PhD students over the last mandate (2 from outside France), and 21 other researchers ranging from postdocs to trainees (including 3 international visiting researchers). The team has also been highly successful obtaining grants, raising1.5 million euros from private funding sources (Fondation Dior, MSD Avenir, Janssen Horizon) as well as French (ANR, France Génomique) and European (Horizon EU) sources. They are a central component of multiple large scale consortia and networks (Elixir, Milieu Intérieur, Horizon) and have very direct links to the clinics, both at Imagine specifically as well as through the SeqOIA program of France Médecine Génomique. The team has done an impressive job of leveraging these resources, where the volume of genome-scale molecular profiling data, the quality of deep clinical annotations, and the buy-in from clinicians to act on their analyses is highly unique. The team has a strong track record both of publications as well as releasing open-source software for the community, authoring a total of eleven publications including two first and five last author (Nature Biotechnology 2021, Genome Biology 2019, Nucleic Acids Research 2021) and releasing multiple open source software tools that are gaining wide spread use in the community (NCBoost, CNVxplorer, Cell-ID). In terms of outreach, the team co-coordinates the graduate school in Translational Bioinformatics at Université Paris-Cité and organises both international conferences (International Society of Computational Biology and European Conference of Computational Biology) and numerous short courses/workshops on various topics. They also serve as scientific advisor for bioinformatics to the SeqOIA program of France Medécine Genomique and have a leadership role in the European Elixir human copy number variation community. The team filed one patent application during the current mandate. The developing focus on novel, decentralised compute architectures both for addressing carbon footprint/climate change effects as well as consent/GDPR limitations are to be recommended.

Weaknesses and risks linked to the context

There is a risk (not necessarily a weakness) of potentially missed opportunities in the valorisation of computational tools developed by the team. It is not clear in the report if there are explicit discussions between the team leader and the Institut leadership/valorisation offices concerning e.g. software licenses, industrial partnerships, etc. Since the team is unique in the institute for being the only completely computational team, we recommend such discussions do take place to make sure informed, intentional decisions are taken.

Analysis of the team's trajectory

The team will build upon their established expertise, extending into new frontiers of linked genomics/EHR mining as well as specific projects on particular rare genetic diseases. The report identifies 10 separate research axes, which seems highly ambitious, but given the number of senior permanent researchers, not unreasonable. On the fundamental computational methods side there is a particular focus on graph-based learning approaches for multi-modal integration and development of federated AI approaches for data security. The specific collaborations on individual diseases are well-motivated by local, complementary expertise and unique resources of Institut Imagine and its partners.

RECOMMENDATIONS TO THE TEAM

The main recommendation of the committee to the team is to continue advancing with the highly productive model for fundamental computational methods development, application in specific scientific/biomedical contexts, and educational leadership that has been established.
We recommend that, if it is not already happening, there be deliberative reflections on how best to valorise the computational tools developed in the team and the scientific discoveries to which they participate.

CONDUCT OF THE INTERVIEWS

Dates

Start: 04 décembre 2023 à 08h45

End: 05 décembre 2023 à 17h00

Interview conducted: on-site or online

INTERVIEW SCHEDULE

December 3th

Arrival of the committee in the afternoon.
Dinner at 20:00

DAY 1, December 4th

8:45 – 9:00
Auditorium
Preliminary meeting of the expert committee (closed hearing)
Attending: expert committee, Scientific Officer (Marie José Stasia, Scientific Officer (SO) and Catherine Etchebest (SO))

9:00 – 9:15
Auditorium
Presentation of the Hcéres evaluation to the unit (Marie José Stasia, SO)
Attending: expert committee, SO, representatives of institutions and all unit members

9:15 – 10:15
Auditorium
Presentation of the research unit by the unit director (including presentation of the trajectory with the future director and 20 min questions)
Attending: expert committee, SO, representatives of institutions and all unit members

10:15 – 10:30
Coffee break (601-602)

10:30 – 12:15
Parallel scientific team presentations (2 sub-committees/3 teams)
35 min/team (15 min presentation + 10 min questions + 5 min with PI + 5 min debriefing of the committee)
Attending: Team members, expert committee, SO, director of Unit, representatives of Institutions
Sub-committee 1 => Auditorium
Team 1: Human genetics of infectious diseases: monogenetic predisposition (J.L. Casanova)
Team 2: Human genetics of infectious diseases: complex predisposition (L. Abel)
Team 3: Embryology & genetics of malformations (J. Amiel)
Sub-committee 2 => 601-602
Team 12: Genetics of mitochondrial diseases (A. Rötig)
Team 13: Genetics of ophthalmologic, auditory and mitochondrial diseases (J.M. Rozet)
Team 17: Heart Morphogenesis (S. Meilhac)

12:15 – 13:30
Lunch: 601-602

13:30 – 15:15
Parallel scientific team presentations (2 sub-committees/3 teams with different SO Marie José Stasia, and Catherine Etchebest)
35 min/team (15 min presentation + 10 min questions + 5 min with PI + 5 min debriefing of the committee)
Attending: Team members, expert committee, SO, director of Unit, representatives of Institutions

Sub-committee 1 : auditorium
Team 9: Intestinal Immunity (N. Cerf-Bensussan)
Team 5: Molecular mechanisms of hematologic disorders and therapeutic implications (O. Hermine)
Team 8: Laboratory of Hereditary Kidney Diseases (S. Saunier)
Sub-committee 2: 601-602
Team 18: Genome Dynamics in the Immune System (**P. Revy & J-P De Villartay)**
Team 21: Chromatin and Gene Regulation during Development (A. Miccio)
Team 22: The Clinical Bioinformatics laboratory (A. Rausell)

15:15 – 15:30 **Coffee break (espace reception au 6ème étage)**

15:30 – 15:45 **Presentation of the platforms (auditorium)**

15:45 – 16:30 **Parallel closed meetings** (3 sub-committees)
- Meeting with thesis students and post-docs: 601-602
Attending: PhD students and postdocs, one sub-committee of experts with the president of the expert committee
- **Meeting with researchers and professors**: **7th floor**
Attending: Researchers except group leaders, one sub-committee of experts, SO
- Meeting with technical and administrative personnel (in French): **auditorium**
Attending: Technicians, Engineers, Administrative staff, one sub-committee of experts, SO

16:30 – 17:30 **Sub-committee debrief** (closed hearing: first "content" draft of the team evaluations/committee) : **601-602 and auditorium**
Expert committees and SOs

17:30 – 18:00 **Committee debrief** (closed hearing: synthesis of sub committees works on the 12 team evaluations): **601-602**
Expert committee and SOs

20:00 **Diner**

DAY 2, December 5th

8:30 – 10:15 **Parallel scientific team presentations** (2 sub-committees/3 teams)
35 min/team (15 min presentation + 10 min questions + 5 min with PI + 5 min debriefing of the committee)
Attending: Team members, expert committee, SO, director of Unit, representatives of Institutions
Sub-committee 1: auditorium
Team 7: Immunogenetics of pediatric autoimmune diseases (F. Rieux-Laucat)
Team 10: Genetic skin diseases: from disease mechanism to therapy (A. Hovnanian)
Team 11: Lymphocyte activation and susceptibility to EBV (S.Latour)
Sub-committee 2: 601-602
Team 14: Molecular and physiopathological bases of osteochondrodysplasia (L. Legeai-Mallet & V. Cormier-Daire)
Team 15: Developmental brain disorders (Vincent Cantagrel)
Team 16: Translational Research for Neurological Disorders (E. Kabashi)

10:15 – 10:30	**Coffee break : (espace reception au 6)**
10:30 - 12:15	**Parallel scientific team presentations** (2 sub-committees/2 teams) 35 min/team (15 min presentation + 10 min questions + 5 min with PI + 5 min debriefing of the committee) *Attending: Team members, expert committee, SO, director of Unit, representatives of Institutions* ***Sub-committee 1: auditorium*** **Team 4: Human lymphohematopoiesis (I. André)** **Team 6: Molecular basis of altered immune homeostasis (G. Menasche & F. Sepulveda)** ***Sub-committee 2: 601-602*** **Team 19: Neurogenetics and neuroinflammation (Y. Crow)** **Team 20: Inflammatory Responses and Transcriptomic Networks in diseases (M. Menager)**
12:15 - 13:30	**Lunch (601-602)**
13:30 – 14:00	***Presentation of new future teams: auditorium*** 15 min/team (10 min presentation + 5 min questions) *Attending: Expert committee, SO, director of Unit, representatives of Institutions and all unit members* **Tissue Immunity in homeostasis and Disease (Bana Jabri)** **Mechanisms and therapy of genetic brain diseases (Michela Deleidi)**
14:00 – 14:30	**Closed Meeting with the representatives of authorities: auditorium** *Attending: expert committee, representatives of Institutions, SO*
14:30 – 15:30	**Closed Meeting of the Committee with the direction of the unit: auditorium** *Attending: Unit Director, director elect, general delegate, directors, executive committee except the PI, expert committee, SO*
15:30 – 17:00	**Final Committee deliberations** (closed hearing, final adjustment to first post visit draft content for the unit and teams)**: 601-602 / coffee break in the room** *Attending: expert committee, SO*

PARTICULAR POINT TO BE MENTIONED

N/A

GENERAL OBSERVATIONS OF THE SUPERVISORS

Université Paris Cité

Le Président

Paris, le 25 Mars 2024

HCERES
2 rue Albert Einstein
75013 Paris

Objet : Rapport d'évaluation de l'unité **DER-PUR250024173 - IHU Imagine - Institut des maladies génétiques.**

Madame, Monsieur,

L'université Paris Cité (UPCité) a pris connaissance du rapport d'évaluation de l'unité IHU Imagine - Institut des maladies génétiques**.**

Présidence

Référence
Pr/DGDRIVE/2023

Affaire suivie par
Christine Debydeal - DGDRIVE

Adresse
85 boulevard St-Germain
75006 - Paris

www.u-paris.fr

Ce rapport a été lu avec attention par la direction de l'unité (cf courriers joints), par le vice-doyen Recherche et le doyen de la Faculté de Santé d'UPCité, par la vice-présidente Recherche d'UPCité et par moi-même. L'ensemble de ces acteurs vous adresse leurs remerciements pour la qualité de ce rapport d'évaluation.

Le doyen de la Faculté de Santé et moi même souhaitons souligner que l'institut Imagine, un des premiers instituts hospitalo-universitaires créés en France, constitue un pôle d'excellence en recherche avec une très forte lisibilité internationale sur les maladies génétiques. Adossé à l'hôpital Necker et à la pointe de la recherche translationnelle, il rassemble à la fois des équipes de recherche, des centres de référence maladies rares et des médecins autour des patients. Il est co-labellisé par Université Paris Cité, l'INSERM et l'APHP, en cohérence avec l'importance donnée à la continuité entre recherche fondamentale et recherche translationnelle au sein de l'institut. Imagine rassemble les acteurs d'un des meilleurs centres intégrés dans le domaine des maladies rares, tout en développant de forts liens avec le monde socio-économique. Il s'appuie sur un scientific advisory board international pour toutes ses décisions scientifiques, en parfaite entente avec l'ensemble des tutelles.

Je vous prie d'agréer, Madame, Monsieur, l'expression de ma considération distinguée.

Édouard Kaminski

Pr Stanislas LYONNET
UMR1163 - Institut *Imagine*
24 Boulevard du Montparnasse
75 015 Paris
FRANCE

Objet : Lettre de réponse au rapport de l'HCERES suite à l'évaluation de l'UMR1163 – Institut Imagine (vague D – 2023/2024)

Nous remercions vivement les présidents et les membres du comité HCERES pour leur travail approfondi et perspicace à l'Institut Imagine, ainsi que pour leurs commentaires et conseils constructifs et perspicaces.

Vous trouverez ci-dessous notre réponse aux points généraux soulevés dans le rapport et aux recommandations adressées à l'unité.

Stanislas LYONNET

HCERES Evaluation - Group D
Campaign 2023 – 2024
UMR1163
Director: Stanislas Lyonnet

Institut des Maladies Génétiques *Imagine*
Research Unit UMR1163 Inserm / Université Paris Cité
Institut Hospitalo-Universitaire (IHU)

Response to the report of the HCERES Committee for the UMR1163 - *Imagine* institute of Genetic Diseases

GENERAL COMMENTS

We deeply thank the chairs and the members of the HCERES committee for their thorough and perceptive work at the *Imagine* Institute, and for their constructive, insightful comments and advice. Below is our response to the points raised in the Report and the recommendations to the unit.

Evaluation area 1: Profile, resources and organization of the unit

About the concern among the permanent staff that they are not informed of important decisions taken by the director and executive committee, we will reinforce our communication process with the diffusion of written reports as suggested, and the recent development of our Intranet.
Concerning the teams that are closing due to retirement or departure of the PI, the direction will accompany the permanent staff as they change teams and settle in, opening case-by-case opportunities.
Finally, regarding the lack of space at in the institute, this is a major concern as we have presented and called it a “crise de croissance”, that we are already addressing through the future re-organization of the laboratories, the day to day practices (shred offices, etc..), the common spaces and the offices. We are supported by an external consultant on this aspect, but also to think about a possible extension of the building (both internal and external).

Evaluation area 2: Attractiveness

For the concern about the cumbersome validation of the *theme leaders* by the SAB, we still feel that it is of the utmost importance, for them, to submit the process by our SAB since that validation offers the possibility to apply to new grants (such as through the FMR or Groupama Foundation).
Concerning the mentoring of young PI, this will be integrated in a more general mentoring process of the young researchers that will be setup during the next contract in association with our on-site human resources.

Evaluation area 3: Scientific production

The adequate position of the contributors in a publication is of course important for the recognition of the work of each and every one. This kind of questions are treated by Inserm through a committee, but also by *Imagine* through the RIS (“referent intégrité scientifique”) of the Institute, and if still needed, the Deontology committee.

Evaluation area 4: Contribution of research activities to society

It would be of interest to know to which tech transfer office this remark refers to. Indeed, as a multi-tutelle institute, we have organized a TTO staff meeting, gathering all parties, with each tech transfer office from: *Imagine*, Inserm (Inserm Transfert), University (DRIVE and the SATT), and APHP (DRCI). *Imagine*'s TTO tries to be the main referent of the PI for the tech transfer to better and more rapidly identify the process adapted to the PI (depending on the employer).

Concerning the report, some of the teams would like to provide a dedicated response to the committee for general comments:

Team 1: Team Casanova

We warmly thank the committee for the very positive evaluation of our team, and we appreciate its support in the recommendations about the challenging question of lab space we need.

With respect to the suggestion in the section "Weaknesses and risks linked to the context", we are developing our interactions with patients' association (e.g. with the association "Vaincre la papillomatose"), and we are increasing our participation in "general public" action and to promote science in schools (e.g. participation at several days organized by the cercle FSER (Fondation Schlumberger pour l'Education et la Recherche))

Team 2: Team Abel

We warmly thank the committee for the very positive evaluation of our team, and do not have any specific comments

Team 6: Team Ménasché / Sepulveda

General comments on the evaluation and the recommendations

"The main weakness is related to the PhD students. PhD students stayed four years in average in the team (two stayed 5 years), which is longer than the recommended 3 years. Their publication level is low: 1.7 original article per student with defended thesis and 0.5 per student as first author."

During this period, 6 PhD students were trained (three stayed 3 years and three stayed 4 four years). Thus, average time to complete their is PhD is 3.5 years. 5 out of 6 PhD students published an article as first author, and several as co-author. The other student without first author paper, the manuscript is in preparation.

- **Isabelle Munoz** 2014-2017 **(3 years)**. IM is currently a post-doctoral researcher associate at the Beavis lab in Melbourne, Autralia.

1. **Munoz, I.,** L. Danelli, J. Claver, N. Goudin, M. Kurowska, I.K. Madera-Salcedo, J.D. Huang, A. Fischer, C. Gonzalez-Espinosa, **G. de Saint Basile**, U. Blank, and **G. Menasche**. 2016a. Kinesin- 1 controls mast cell degranulation and anaphylaxis through PI3K-dependent recruitment to the granular Slp3/Rab27b complex. **J Cell Biol** 215:203-216. https://doi.org/10.1083/jcb.201605073

2. F. Adam, A. Kauskot, **M. Kurowska**, N. Goudin, **I. Munoz**, J.C. Bordet, J.D. Huang, A. Fischer, D. Borgel, **G. de Saint Basile**, O.D. Christophe, **G. Ménasché**. Kinesin-1 regulates platelet secretion and thrombus stability by interacting with the granule Slp4/Rab27b effector complex. **ATVB** 2018, May;38(5):1037-1051. https://doi.org/10.1161/ATVBAHA.117.310373

- **Claire Leveau** 2014-2018 **(4 years)**. CL is currently a post-doctoral researcher associate at the Venteclef lab in Paris, France.

1. **Leveau C**, Gajardo T, **El-Daher MT**, Cagnard N, Fischer A, **de Saint Basile G**, **Sepulveda FE**. Ttc7a regulates hematopoietic stem cell functions while controlling the stress-induced response. **Haematologica**. 2020 Jan;105(1):59-70. https://doi.org/10.3324/haematol.2018.207100
2. **Tania Gajardo**, **Marie Lô**, Mathilde Bernard, **Claire Leveau**, **Marie-Thérèse El-Daher**, **Mathieu Kurowska**, Gregoire Le Lay, Despina Moshous, Bénédicte Neven, Alain Fischer, **Gaël Ménasché**, **Geneviève de Saint Basile**, Pablo Vargas, **Fernando E. Sepulveda**. Actin dynamics regulation by TTC7A/PI4KIIIα limits DNA damage and cell death under confinement. J Allergy Clin Immunol. 2023 Jun 29:S0091-6749(23)00838-2. doi: 10.1016/j.jaci.2023.06.016.
3. **El-Daher MT**, Lemale J, Bruneau J, **Leveau C**, **Guerin F**, Lambert N, Diana JS, Neven B, **Sepulveda FE**, Coulomb-L'Hermine A, Molina T, Picard C, Fischer A, **de Saint Basile G.** Chronic Intestinal Pseudo-Obstruction and Lymphoproliferative Syndrome as a Novel Phenotype Associated With Tetratricopeptide Repeat Domain 7A Deficiency. **Front Immunol**. 2019 Nov 7;10:2592. https://doi.org/10.3389/fimmu.2019.02592
4. **El-Daher MT**, Cagnard N, Gil M, Da Cruz MC, **Leveau C**, **Sepulveda F**, Zarhrate M, Tores F, Legoix P, Baulande S, de Villartay JP, Almouzni G, Quivy JP, Fischer A, **de Saint Basile G.** Tetratricopeptide repeat domain 7A is a nuclear factor that modulates transcription and chromatin structure. **Cell Discov.** 2018 Nov 13;4:61. https://doi.org/10.1038/s41421-018-0061-y
5. Leclerc-Mercier, S., R. Lemoine, A.E. Bigorgne, **F. Sepulveda**, **C. Leveau**, A. Fischer, N. Mahlaoui, S. Hadj-Rabia, and **G. de Saint Basile**. 2016. Ichthyosis as the dermatological phenotype associated with TTC7A mutations. *Br J Dermatol* 175:1061-1064.

- **Meriem Belabed** 2016-2019 **(3 years)**. MB is currently a post-doctoral researcher associate at the Merad lab in New York, US.

1. **Belabed M**, Mauvais FX, **Maschalidi S**, **Kurowska M**, Goudin N, Huang JD, Fischer A, **de Saint Basile G**, van Endert P, **Sepulveda FE**, **Ménasché G.** Kinesin-1 regulates antigen cross-presentation through the scission of tubulations from early endosomes in dendritic cells. **Nat Commun**. 2020 Apr 14;11(1):1817. https://doi.org/10.1038/s41467-020-15692-0

- **Cyril Longé** 2017-2021 **(4 years)**. CL is currently flow cytometry scientist at Miltenyi Biotec (Paris, France).

1. **Longé C.**, Bratti M., **Kurowska M**, Vibhushan S., David P, Desmeure V., Huang JD, Fischer A, **de Saint Basile G**, **Sepulveda FE**, Blank U., **Ménasché G.** Rab44 regulates murine mast cell-driven anaphylaxis through kinesin-1-dependent secretory granule translocation. **J Allergy Clin Immunol.** 2022 Sep;150(3):676-689. https://doi.org/10.1016/j.jaci.2022.04.009
2. Bratti M, Vibhushan S, Longé C, Koumantou D, **Ménasché G**, Benhamou M, Varin-Blank N, Blank U, Saveanu L, Ben Mkaddem S. Insulin-regulated aminopeptidase contributes to setting the intensity of FcR-mediated inflammation. Front Immunol. 2022 Oct 27;13:1029759. https://doi.org/10.3389/fimmu.2022.1029759

- **Tania Gajardo** 2017-2021 **(4 years)**. TG is currently research scientist at the Egle Therapeutics (Paris, France).

1. **Tania Gajardo**, **Marie Lô**, Mathilde Bernard, **Claire Leveau**, **Marie-Thérèse El-Daher**, **Mathieu Kurowska**, Gregoire Le Lay, Despina Moshous, Bénédicte Neven, Alain Fischer, **Gaël Ménasché**, **Geneviève de Saint Basile**, Pablo Vargas, **Fernando E. Sepulveda**. Actin dynamics regulation by TTC7A/PI4KIIIα limits DNA damage and cell death under confinement. J Allergy Clin Immunol. 2023 Jun 29:S0091-6749(23)00838-2. doi: 10.1016/j.jaci.2023.06.016.
2. Neehus, A.L., B. Carey, M. Landekic, **P. Panikulam**, G. Deutsch, M. Ogishi, C.A. Arango-Franco, Q. Philippot, M. Modaresi, I. Mohammadzadeh, M. Corcini Berndt, D. Rinchai, T. Le Voyer, J. Rosain, M. Momenilandi, M. Martin-Fernandez, T. Khan, J. Bohlen, J.E. Han, A. Deslys, M. Bernard, **T. Gajardo-Carrasco**, C. Soudee, C. Le Floc'h, M. Migaud, Y. Seeleuthner, M.S. Jang, E. Nikolouli, S. Seyedpour, H. Begueret, J.F. Emile, P. Le Guen, G. Tavazzi, C.N.J. Colombo, F.C. Marzani, M. Angelini, F. Trespidi, S. Ghirardello, N. Alipour, A. Molitor, R. Carapito, M. Mazloomrezaei, H. Rokni-Zadeh, M. Changi-Ashtiani, C. Brouzes, P. Vargas, A. Borghesi, N. Lachmann, S. Bahram, B. Crestani, S. Pahari, L.S. Schlesinger, N. Marr, D. Bugonovic, S. Boisson-Dupuis, V. Beziat, L. Abel, R. Borie, L.R. Young, R. Deterding, M. Shahrooei, N. Rezaei, N. Parvaneh, D. Craven, P. Gros, D. Malo**, F.E. Sepulveda**, L.M. Nogee, N. Aladjidi, B.C. Trapnell, J.L. Casanova, and J. Bustamante. 2024. Human inherited CCR2 deficiency underlies progressive polycystic lung disease. *Cell* 187:390-408 e323.
3. C Boussard, L Delage, **T Gajardo**, A Kauskot, M Batignes, N Goudin, C Brunaud, B Durel, Q Riller, M Moya-Nilges, J Solarz, C Repérant, JC Bordet, **P Panikulam**, MC Stolzenberg, O Pellé, C Lebreton, A Magérus, V Pirabakaran, P Vargas, S Dupichaud, A Vinit, M Zarhrate, C Masson, N Aladjidi, PD Arkwright, B Bader-Meunier, S Baron Joly, J Benadiba, E Bernard, D Berrebi, C Bodemer, M Castelle, F Charbit-Henrion, M Chbihi, A Debray, P Drabent, S Fraitag, M Hié, J Landmann-Parker, L Lhermitte, D Moshous, P Rohrlich, F Ruemmele, A Welfringer-Morin, M Tusseau, A Belot, N Cerf-Bensussan, M Roelens, C Picard, B Neven, A Fischer, I Callebaut, M Ménager, **FE Sepulveda**, F Adam, F Rieux-Laucat. DOCK11 deficiency in patients with X-linked actinopathy and autoimmunity. Co-last author. Blood. 2023 Jun 1;141(22):2713-2726. doi: 10.1182/blood.2022018486.
4. Gross, M., C. Speckmann, A. May, **T. Gajardo-Carrasco**, K. Wustrau, S.L. Maier, M. Panning, D. Huzly, A. Agaimy, Y.T. Bryceson, S. Choo, C.W. Chow, G. Duckers, A. Fasth, S. Fraitag, K. Grawe, S. Haxelmans, D. Holzinger, O. Hudowenz, J.M. Hubschen, C. Khurana, K. Kienle, R. Klifa, K. Korn, H. Kutzner, T. Lammermann, S. Ledig, D. Lipsker, M. Meeths, N. Naumann-Bartsch, J. Rascon, A. Schanzer, M. Seidl, B. Tesi, C. Vauloup-Fellous, B. Vollmer-Kary, K. Warnatz, C. Wehr, B. Neven, P. Vargas, **F.E. Sepulveda**, K. Lehmberg, A. Schmitt-Graeff, and S. Ehl. 2022. Rubella vaccine-induced granulomas are a novel phenotype with incomplete penetrance of genetic defects in cytotoxicity. *J Allergy Clin Immunol* 149:388-399 e384.
5. **Leveau C**, **Gajardo T**, **El-Daher MT**, Cagnard N, Fischer A, **de Saint Basile G**, **Sepulveda FE**. Ttc7a regulates hematopoietic stem cell functions while controlling the stress-induced response. **Haematologica**. 2020 Jan;105(1):59-70. https://doi.org/10.3324/haematol.2018.207100

- **Valère Desmeure** 2019-2023 **(3 years).**
Valère Desmeure, **Mathieu Kurowska**, Fabienne Jabot-Hanin, Pierre David, **Fernando E. Sepulveda**, Alain Fischer, **Geneviève de Saint Basile**, Rola Abou-Taam, Andrey V. Kajava, **Guillaume Lezmi**, **Gaël Ménasché**. Mutation in BiP co-chaperone DNAJC25 is associated with severe allergic asthma. **In preparation**

"Similarly, postdoc publication level is very low (two without publication and two with no publication as first author)."

During this period, 5 post-doctoral researchers have been part of the team. All the post-doctoral fellows published at least two articles except Manon Gourdelier who completed just one year in the laboratory due to personal reasons.

- **Manon Gourdelier** (janv 2023-Janv 2024) left **after one year for personal reasons.**

- **Sara Mouasni** (Fev 2019-Aug 2022) **got 2 publication as co-author.**

1. Soudais, C., R. Schaus, C. Bachelet, N. Minet**, S. Mouasni**, C. Garcin, C.L. Souza, P. David, C. Cousu, H. Asnagli, A. Parker, P. Palmquist-Gomes, **F.E. Sepulveda**, S. Storck, S.M. Meilhac, A. Fischer, E. Martin, and S. Latour. 2024. Inactivation of cytidine triphosphate synthase 1 prevents fatal auto-immunity in mice. *Nat Commun* 15:1982.
2. Thoidingjam LK, Blouin CM, Gaillet C, Brion A, Solier S, Niyomchon S, El Marjou A, **Mouasni S**, **Sepulveda FE**, **de Saint Basile G**, Lamaze C, Rodriguez R. Small Molecule Inhibitors of Interferon-Induced JAK-STAT Signalling. Angew Chem Int Ed Engl. 2022 Aug 8;61(32):e202205231. doi: 10.1002/anie.202205231. https://doi.org/10.1002/anie.202205231

- **Tania Gajardo** (Dec 2021 – Aug 2022) **got 5 publications including one as first author.**

1. **Tania Gajardo**, **Marie Lô**, Mathilde Bernard, **Claire Leveau**, **Marie-Thérèse El-Daher**, **Mathieu Kurowska**, Gregoire Le Lay, Despina Moshous, Bénédicte Neven, Alain Fischer, **Gaël Ménasché**, **Geneviève de Saint Basile**, Pablo Vargas, **Fernando E. Sepulveda**. Actin dynamics regulation by TTC7A/PI4KIIIα limits DNA damage and cell death under confinement. J Allergy Clin Immunol. 2023 Jun 29:S0091-6749(23)00838-2. doi: 10.1016/j.jaci.2023.06.016.
2. Neehus, A.L., B. Carey, M. Landekic, **P. Panikulam**, G. Deutsch, M. Ogishi, C.A. Arango-Franco, Q. Philippot, M. Modaresi, I. Mohammadzadeh, M. Corcini Berndt, D. Rinchai, T. Le Voyer, J. Rosain, M. Momenilandi, M. Martin-Fernandez, T. Khan, J. Bohlen, J.E. Han, A. Deslys, M. Bernard, **T. Gajardo-Carrasco**, C. Soudee, C. Le Floc'h, M. Migaud, Y. Seeleuthner, M.S. Jang, E. Nikolouli, S. Seyedpour, H. Begueret, J.F. Emile, P. Le Guen, G. Tavazzi, C.N.J. Colombo, F.C. Marzani, M. Angelini, F. Trespidi, S. Ghirardello, N. Alipour, A. Molitor, R. Carapito, M. Mazloomrezaei, H. Rokni-Zadeh, M. Changi-Ashtiani, C. Brouzes, P. Vargas, A. Borghesi, N. Lachmann, S. Bahram, B. Crestani, S. Pahari, L.S. Schlesinger, N. Marr, D. Bugonovic, S. Boisson-Dupuis, V. Beziat, L. Abel, R. Borie, L.R. Young, R. Deterding, M. Shahrooei, N. Rezaei, N. Parvaneh, D. Craven, P. Gros, D. Malo**, F.E. Sepulveda**, L.M. Nogee, N. Aladjidi, B.C. Trapnell, J.L. Casanova, and J. Bustamante. 2024. Human inherited CCR2 deficiency underlies progressive polycystic lung disease. *Cell* 187:390-408 e323.
3. C Boussard, L Delage, **T Gajardo**, A Kauskot, M Batignes, N Goudin, C Brunaud, B Durel, Q Riller, M Moya-Nilges, J Solarz, C Repérant, JC Bordet, **P Panikulam**, MC Stolzenberg, O Pellé, C Lebreton, A Magérus, V Pirabakaran, P Vargas, S Dupichaud, A Vinit, M Zarhrate, C Masson, N Aladjidi, PD Arkwright, B Bader-Meunier, S Baron Joly, J Benadiba, E Bernard, D Berrebi, C Bodemer, M Castelle, F Charbit-Henrion, M Chbihi, A Debray, P Drabent, S Fraitag, M Hié, J Landmann-Parker, L Lhermitte, D Moshous, P Rohrlich, F Ruemmele, A Welfringer-Morin, M Tusseau, A Belot, N Cerf-Bensussan, M Roelens, C Picard, B Neven, A Fischer, I Callebaut, M Ménager, **FE Sepulveda**, F Adam, F Rieux-Laucat. DOCK11 deficiency in patients with X-linked actinopathy and autoimmunity. Co-last author. Blood. 2023 Jun 1;141(22):2713-2726. doi: 10.1182/blood.2022018486.

4. Gross, M., C. Speckmann, A. May, **T. Gajardo-Carrasco**, K. Wustrau, S.L. Maier, M. Panning, D. Huzly, A. Agaimy, Y.T. Bryceson, S. Choo, C.W. Chow, G. Duckers, A. Fasth, S. Fraitag, K. Grawe, S. Haxelmans, D. Holzinger, O. Hudowenz, J.M. Hubschen, C. Khurana, K. Kienle, R. Klifa, K. Korn, H. Kutzner, T. Lammermann, S. Ledig, D. Lipsker, M. Meeths, N. Naumann-Bartsch, J. Rascon, A. Schanzer, M. Seidl, B. Tesi, C. Vauloup-Fellous, B. Vollmer-Kary, K. Warnatz, C. Wehr, B. Neven, P. Vargas, **F.E. Sepulveda**, K. Lehmberg, A. Schmitt-Graeff, and S. Ehl. 2022. Rubella vaccine-induced granulomas are a novel phenotype with incomplete penetrance of genetic defects in cytotoxicity. *J Allergy Clin Immunol* 149:388-399 e384.
5. **Leveau C**, **Gajardo T**, **El-Daher MT**, Cagnard N, Fischer A, **de Saint Basile G**, **Sepulveda FE**. Ttc7a regulates hematopoietic stem cell functions while controlling the stress-induced response. **Haematologica**. 2020 Jan;105(1):59-70. https://doi.org/10.3324/haematol.2018.207100

- **Marie Thérèse El Daher** (oct 2013-Oct 2018) **got 3 publications including two as first author.**

1. Leveau C, Gajardo T, **El-Daher MT**, Cagnard N, Fischer A, **de Saint Basile G**, **Sepulveda FE**. Ttc7a regulates hematopoietic stem cell functions while controlling the stress-induced response. **Haematologica**. 2020 Jan;105(1):59-70. https://doi.org/10.3324/haematol.2018.207100
2. **El-Daher MT**, Lemale J, Bruneau J, Leveau C, **Guerin F**, Lambert N, Diana JS, Neven B, **Sepulveda FE**, Coulomb-L'Hermine A, Molina T, Picard C, Fischer A, **de Saint Basile G.** Chronic Intestinal Pseudo-Obstruction and Lymphoproliferative Syndrome as a Novel Phenotype Associated With Tetratricopeptide Repeat Domain 7A Deficiency. **Front Immunol**. 2019 Nov 7;10:2592. https://doi.org/10.3389/fimmu.2019.02592
3. **El-Daher MT**, Cagnard N, Gil M, Da Cruz MC, Leveau C, **Sepulveda F**, Zarhrate M, Tores F, Legoix P, Baulande S, de Villartay JP, Almouzni G, Quivy JP, Fischer A, **de Saint Basile G.** Tetratricopeptide repeat domain 7A is a nuclear factor that modulates transcription and chromatin structure. **Cell Discov.** 2018 Nov 13;4:61. https://doi.org/10.1038/s41421-018-0061-y

- **Sophia Maschalidi** (Sept 2012- March 2017) **got 9 publications including two as first author.**

1. Belabed M, Mauvais FX, **Maschalidi S**, **Kurowska M**, Goudin N, Huang JD, Fischer A, **de Saint Basile G**, van Endert P, **Sepulveda FE**, **Ménasché G.** Kinesin-1 regulates antigen cross-presentation through the scission of tubulations from early endosomes in dendritic cells. **Nat Commun**. 2020 Apr 14;11(1):1817. https://doi.org/10.1038/s41467-020-15692-0
2. Mosa MH, Nicolle O, **Maschalidi S**, **Sepulveda FE**, Bidaud-Meynard A, Menche C, Michels BE, Michaux G, **de Saint Basile G***, Farin HF*. Dynamic Formation of Microvillus Inclusions During Enterocyte Differentiation in Munc18-2-Deficient Intestinal Organoids. **Cell Mol Gastroenterol Hepatol.** 2018 Aug 14;6(4):477-493.e1. https://doi.org/10.1016/j.jcmgh.2018.08.001 *Co last and Co corresponding
3. **Maschalidi S**, Nunes-Hasler P, Nascimento CR, Sallent I, Lannoy V, Garfa-Traore M, Cagnard N, **Sepulveda FE**, Vargas P, Lennon-Duménil AM, van Endert P, Capiod T, Demaurex N, Darrasse-Jèze G, Manoury B. UNC93B1 interacts with the calcium sensor STIM1 for efficient antigen cross-presentation in dendritic cells. **Nat Commun**. 2017 Nov 21;8(1):1640. https://doi.org/10.1038/s41467-017-01601-5
4. Babdor, J., D. Descamps, A.C. Adiko, M. Tohme, **S. Maschalidi**, I. Evnouchidou, L.R. Vasconcellos, M. De Luca, F.X. Mauvais, M. Garfa-Traore, M.M. Brinkmann, M. Chignard, B. Manoury, and L. Saveanu. 2017. IRAP(+) endosomes restrict TLR9 activation and signaling. Nat Immunol 18:509-518. DOI: 10.1038/ni.3711
5. Nunes-Hasler, P., **S. Maschalidi**, C. Lippens, C. Castelbou, S. Bouvet, D. Guido, F. Bermont, E.Y. Bassoy, N. Page, D. Merkler, S. Hugues, D. Martinvalet, B. Manoury, and N. Demaurex. STIM1 promotes

migration, phagosomal maturation and antigen cross-presentation in dendritic cells. **Nat Commun** 2017. 8:1852. https://doi.org/10.1038/s41467-017-01600-6

6. **Sepulveda, F.E.**, A. Garrigue, **S. Maschalidi**, M. Garfa-Traore, **G. Menasche**, A. Fischer, and **G. de Saint Basile**. 2016. Polygenic mutations in the cytotoxicity pathway increase susceptibility to develop HLH immunopathology in mice. *Blood* 127:2113-2121. doi: 10.1182/blood-2015-12-688960

7. **Maschalidi, S.**, **F.E. Sepulveda**, A. Garrigue, A. Fischer, and **G. de Saint Basile**. 2016. Therapeutic effect of JAK1/2 blockade on the manifestations of hemophagocytic lymphohistiocytosis in mice. *Blood* 128:60-71. doi: 10.1182/blood-2016-02-700013

8. **Sepulveda, F.E.**, **S. Maschalidi,** C.A. Vosshenrich, A. Garrigue, M. Kurowska, **G. Menasche**, A. Fischer, J.P. Di Santo, and **G. de Saint Basile**. 2015b. A novel immunoregulatory role for NK- cell cytotoxicity in protection from HLH-like immunopathology in mice. *Blood* 125:1427-1434. doi: 10.1182/blood-2014-09-602946.

9**. de Saint Basile, G**., **F.E. Sepulveda**, **S. Maschalidi**, and A. Fischer. 2015. Cytotoxic granule secretion by lymphocytes and its link to immune homeostasis. *F1000Res* 4:930. Doi: 10.12688/f1000research.6754.1

"Nat Genet as co-authors"

The Nat Genet publication is not as co-authors but co-leader article (ie first and corresponding authors).

Gayden T*, **Sepulveda FE***, Khuong-Quang DA, Pratt J, Valera ET, **Garrigue A**, Kelso S, Sicheri F, Mikael LG, Hamel N, Bajic A, Dali R, Deshmukh S, Dervovic D, Schramek D, **Guerin F**, Taipale M, Nikbakht H, Majewski J, Moshous D, Charlebois J, Abish S, Bole-Feysot C, Nitschke P, Bader-Meunier B, Mitchell D, Thieblemont C, Battistella M, Gravel S, Nguyen VH, Conyers R, Diana JS, McCormack C, Prince HM, Besnard M, Blanche S, Ekert PG, Fraitag S, Foulkes WD, Fischer A, Neven B, Michonneau D, **de Saint Basile G****, Jabado N**. Germline HAVCR2 mutations altering TIM-3 characterize subcutaneous panniculitis-like T cell lymphomas with hemophagocytic lymphohistiocytic syndrome. **Nat Genet.** 2018 Dec;50(12):1650-1657. https://doi.org/10.1038/s41588-018-0251-4. *Co-first author, **Co-last author, **Co-corresponding author.

"Outreach to lay public is limited."

Since 2017, 6 middle and high school students (Harris Albouchi 2022, Raphaël Maillard 2022, Juliette Maingreaud 2021, Hugo Qiu 2018, Charles Jean-François 2018, Eliot Giot-Mikkelsen 2017) were welcomed into the lab for an observation internship. The welcome of these trainees is organized by Mathieu Kurowska or our PhD students. They familiarize these young recruits with the scientific approach while respecting the principles of integrity and ethics. In addition, members of our team have participated to several communications and manifestations in the framework of "LHF espoir" association, that raises funds for research projects on HLH disorders.

Team 7: Team Rieux-Laucat

General comments on the evaluation and the recommendations

Recommendation: Considering that the team leader will retire after the end of the next contract, we strongly recommend to plan ahead to ensure completion of ongoing projects and continuity with the new leadership.

This has been taken into accounts with the recruitment of a researcher (Marianna Parlatto) with a permanent position (CRCN INSERM) who moved from Team 13 to our team. Together with Pr Benedicte Neven (PUPH) and Aude Magerus, they will ensure continuity for a new leadership that will be decided before the midterm of the 2025-2029 contract.

Team 14: Team Hovnanian

The result of **Evaluation area 4, Contribution of Research Activities to Society** is listed as a strength, but also as a weakness in the HCERES report. We personally believe it is a strength of our laboratory. Please amend.

Comment on **Recommendation to the team:**

Following the new French Law allowing University Professors to be maintained in function until 70 year of age, Prof. Alain Hovnanian has submitted in February 2024, a separate application to INSERM (Structure vague D) to renew the leadership of his research team from 2025 to 2029 (Prof. Hovnanian will be 70-year-old in May 2029).

These 5 extra years (2025-2029) will enable the team to conclude on-going projects and to recruit the required (and already funded) postdocs via international channels. These years will also be used to increase the collaboration and to initiate new projects with Team 1 (Human genetics of infectious diseases led by Prof. JL Casanova), and to prepare the team's succession after 2029.

Team 15: Team Kabashi

We would like to thank the HCERES committee for their insightful and encouraging comments. As suggested by the committee to maintain an excellent research standard and to sustain our growth trajectory, we are actively recruiting young researchers, with 5 postdocs and 5 PhD students currently enrolled and ongoing recruitments for young researchers funded by the RHU programme as well as ongoing national and European grants. Importantly, to increase the presence of permanent staff, Dr. de Calbiac has applied for the Inserm concours and Dr. Raas will apply in early 2025. Also, clinical researchers from the CHU-Necker are expected to join the team in early 2025.

Team 20: Team Ménager

I would like to thank the members of the HCERES evaluation committee. Regarding the recommendations to the team, I fully agree and also came to the same conclusions.

For the moment, the research team is lacking some permanent staff position in order to make sure to maintain some competitive research activity. One candidate has been identified in my team and as pointed out by the committee, we will keep prioritizing the scientific impact of publications to obtain permanent positions and attract additional high-level profiles. I wish the team could have been reinforced by people with permanent positions, during the recent restructuration among several teams at Imagine.

It is also true that, myself and some members of my team, have invested significant amount of time and resources for the creation and the development of the LabTech single-cell@Imagine. Now to allow to account both for the growing demands (needs from researchers) and the appearance of new technologies, we should think of significantly strengthened the LabTech, both in terms of human

resources (at the bench and for computational analyses) and equipment to maintain its level of prestation of services and research and development.

Although, members of the research teams and the LabTech should still be embedded in the same "team", as proposed by the HCERES committee, hiring a senior permanent staff to assist the PI in the management of the LabTech, in addition of reinforcing both wet and dry part (for research and development) is required to maintain both the level of attractiveness and competitivity of the team, while providing fine-tuned up to date services to academic researchers at Imagine but not only (the LabTech being a 10X genomics certified provider).

Team 21: Team Miccio

We thank the committee for their positive evaluation and the following recommendation:

"The team has an outstanding progression but would have to take care of the theme leaders and project managers within the team to guarantee a long term stability and follow up to all the projects."

Regarding the above-mentioned recommendation, we would like to highlight that:

- Dr. Six will apply in 2024 to the Imagine theme leader position and later to the DR2 INSERM position.
- A senior postdoc in the lab (Dr. Megane Brusson) has applied this year for a researcher INSERM position.
- The project manager is associated with the activity of the team has a permanent position (covered by the EDITSCD HORIZON grant for the next 4 years).

Team 22: Team Rausell

General comments on the evaluation and the recommendations

General comments: We thank the HCERES panel for the positive evaluation and insightful recommendations.

Specific comments:

Regarding the section: "*Weaknesses and risks linked to the context:* There is a risk (not necessarily a weakness) of potentially missed opportunities in the valorisation of computational tools developed by the team. It is not clear in the report if there are explicit discussions between the team leader and the Institut leadership/valorisation offices concerning e.g. software licenses, industrial partnerships, etc. Since the team is unique in the institute for being the only completely computational team, we recommend such discussions do take place to make sure informed, intentional decisions are taken.

ANSWER: We thank the review panel for pointing out this question. We hereby confirm that the laboratory of Clinical Bioinformatics works in close and regular interaction with the *Imagine*'s Department of Innovation and Valorisation (DIVA) as well as with the Bioentrepreneur program of the Institute. Each of our software innovations were evaluated for their potential valorisation. Of note, the laboratory commitment with open and reproducible science led us to release all our software as open-source with GPL licences and to freely distribute them to the community through Bioconductor packages, Github repositories and Docker images, following standard practices of alternative state-of-the-art methods in the research areas of the laboratory.

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