Research evaluation

EVALUATION REPORT OF THE UNIT

INEM - Institut Necker enfants malades - centre de recherche

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

Centre national de la recherche scientifique - CNRS

EVALUATION CAMPAIGN 2023-2024

GROUP D

Report published on July, 01 2024

High Council for evaluation of research and hgher education

In the name of the expert committee:

Philippe Pierre, Chairman 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 chairs 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

Chairman: Mr Philippe Pierre, CNRS Marseille

Experts:

Ms Ariela Benigni, Istituto di Ricerche Farmacologiche Mario Negri IRCCS Italia
Mr Michel Cogne, Université de Rennes
Ms Pilar Dominguez, Inserm Rennes
Ms Marika Maria Caterina Falcone, Ospedale San Raffaele SRL Italie
Ms Patricia Gaspar, Inserm, Paris
Mr Pablo Giacobini, Inserm, Lille
Ms Caroline Goujon, CNRS, Montpellier
Mr Christophe Leroyer, Université de Bretagne Occidentale, Brest
Mr Jacques Neefjes, Netherlands Cancer Institute, Pays-Bas
Mr Eric Oswald, Université Paul Sabatier Toulouse and CHU de Toulouse
(Following the interviews, Mr Jean-Claude Sirard, Inserm, Lille, has recused himself from being expert)
Mr Iannis Talianidis, vice-chairman of the committee, Institute of Molecular Biology and Biotechnology, Forth Grèce
(Following the interviews, Ms Nathalie Vergnolle, Inserm, Toulouse, has recused herself from being expert)
Mr Adrian Woolf University of Manchester, United Kingdom

HCÉRES REPRESENTATIVE

Mr Cyrille Colin

REPRESENTATIVES OF SUPERVISING INSTITUTIONS AND BODIES

Ms Chantal Boulanger, Inserm
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Ms Christine Guillard, Université Paris Cité
Ms Claire de Margerye, Inserm
Mr Matthieu Resche Rigon, Université Paris Cité
Mr Philippe Rusniewski, Université Paris Cité
Mr Michel Vidal, Université Paris Cité

CHARACTERISATION OF THE UNIT

- Name: Institut Necker Enfants Malades
- Acronym: INEM
- Label and number: Inserm UP Cité U1151 and CNRS UMR8254
- Composition of the executive team:

Director: Fabiola TERZI
General Secretary: Sabine BARBUT
Directors of the "Growth and Signalling" Department: Mario PENDE, Marco PONTOGLIO,
Directors of the Immunology, Infectiology, Haematology (I2H) Department: Simon FILLATREAU, Peter VAN ENDERT

SCIENTIFIC PANELS OF THE UNIT

SVE Sciences du vivant et environnement
Panel 1
SVE6: Human Physiology and Physiopathology, Ageing
Panel 2
SVE4: Immunity, Infection and Immunotherapy
Panel 3
SVE3: Living Molecules, Integrative Biology (From Genes and Genomes to Systems), Cell and Development Biology for Animal Science
Panel 4
SVE5: Neurosciences and Nervous System Disorders

THEMES OF THE UNIT

The Unit is focusing on human pathophysiological conditions, including chronic diseases, metabolic syndromes, as well as immunological disorders. The 21 teams forming INEM have a strong translational component in all areas of their activities, covering the entire landscape from basic research to clinical studies.

HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

The Institut Necker-Enfants Malades (INEM) is an internationally recognized biomedical research center established in January 2014. It is located in the Necker campus, which comprises the Hospital Necker Enfants Malades, the Institut Imagine dedicated to genetic diseases, the SFR Necker and the Institut Necker Enfants Malades. Prior to January 2014, the research laboratories in the Necker campus were independent units scattered across various buildings with limited connections between them. The restructuring process began with the renovation of the Medical School building in 2015, providing an opportunity for these research units to be consolidated in a single building, giving rise to the formation of the INEM. During the renovation period, the INEM research teams were temporarily housed in facilities on the Necker hospital campus and the former Broussais hospital. In the fall of 2019, all of the research teams were finally brought together in a new building in the Necker campus, fostering collaboration and establishing an organizational structure favorable to develop the Institut Necker Enfants Malades a leading biomedical research center in Europe. INEM is structured in two departments: the department of "Growth and Signalling" and the department of Immunology, Infectiology, Haematology, comprising ten and eleven teams, respectively.

RESEARCH ENVIRONMENT OF THE UNIT

The "Cell biology: Growth and Signalling" department (coordinated by Mario Pende and Marco Pontoglio) focuses on studying the growth, signaling and metabolic adaptations associated with a number of human pathophysiological conditions, including chronic kidney diseases, cancer and overgrowth syndromes, metabolic syndromes, lysosomal storage diseases, neurocognitive impairment, cystic fibrosis, aging, and sarcopenia. In a close collaboration with the Hospital, the group leaders apply their internationally recognized knowledge on the fundamental biological processes of cell cycle, autophagy, mitochondrial dynamics, hormone-growth factor-nutrient signal transduction, transcriptional networks and epigenetics. The I2H department (coordinated by Simon Fillatreau and Peter Van Endert) brings together immunologists, microbiologists and haematologists. I2H scientists have a strong track record in major fields such as normal and pathological B and T cell responses to pathogens and vaccines, autoimmunity, physiological and therapeutic immuno-regulation, antigen presentation cell biology, pathogenesis of systemic infections and microbiota. The department continuously adapts to integrate

frontier research, e.g. by recruiting young groups working on systems biology applied to host-pathogen interaction or leucocyte mobility, and by developing transdisciplinary approaches with scientists from the "Growth and Signalling department" studying metabolism, autophagy and regulation of cell growth. In addition, The Necker campus benefits from several shared core facilities administered by the "Structure Fédérative de Recherche" (SFR) Necker (INSERM US24/CNRS UMS3633). These facilities are supported by the two research institutes on the Necker campus, Imagine Institute and INEM. Furthermore, the Necker campus encourages close collaboration and interaction with the "Necker Enfants Malades" hospital. This hospital hosts various pediatric medical and surgical specialties, a maternity ward, as well as highly specialized adult services in nephrology, renal transplantation, hematology, and infectious diseases. With nearly 31 rare diseases centers and expertise in severe or complex pathologies, the clinical teams at the hospital have developed a strong synergy with the research units and the SFR Necker at the Necker campus.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	25
Maîtres de conférences et assimilés	24
Directeurs de recherche et assimilés	15
Chargés de recherche et assimilés	17
Personnels d'appui à la recherche	48
Sous-total personnels permanents en activité	**129**
Enseignants-chercheurs et chercheurs non permanents et assimilés	18
Personnels d'appui non permanents	50
Post-doctorants	37
Doctorants	64
Sous-total personnels non permanents en activité	**169**
Total personnels	**298**

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
UNIVERSITÉ PARIS-CITÉ	47	0	15
INSERM	0	26	20
AUTRES	2	0	9
CNRS	0	6	4
Total personnels	**49**	**32**	**48**

GLOBAL ASSESSMENT

***The global performance of the INEM unit is* excellent to *outstanding*.**

INEM has consistently excelled in scientific production during its recent mandate, publishing original research articles in esteemed journals across physiopathology and immunology. The unit has proactively addressed

previous recommendations by enhancing its workforce, introducing several new team leaders. These team leaders have exhibited promising potential, establishing themselves as key contributors in their respective fields through publications in prestigious journals and successful funding acquisition. The commitment to fostering collaboration is evident in INEM's strong intramural partnerships and extensive networks on both national and global scales. The unit's research activities are well-supported by substantial funding from national and international public and private bodies, including several grants from the European Research Council. Additionally, INEM benefits from cutting-edge technological platforms, shared with the neighboring institute IMAGINE, which are organized under a 'Structure federative de Recherche' framework. INEM's outstanding status in translational research is affirmed by the active involvement of clinicians in most teams and the FDA approval of therapeutic approaches originating from INEM's research. The unit comprises exceptional research teams that collectively contribute to the high-quality research produced and published. The committee was pleased with the quality of the presentations by the different group leaders and the breadth of the results presented. Overall, the different staff categories present during the visit are extremely pleased to work at INEM and praise its organization.

While INEM is poised for a positive transformation with the reshuffling of teams, there is uncertainty regarding the impact on the careers of permanent researchers, graduate students, engineers, and technicians involved in these changes. To navigate this transition effectively, a call for increased transparency in decision-making processes and enhanced top-down communication with personnel is emphasized. Closer mentoring by the scientific direction and team leaders, especially for permanent staff, is recommended to facilitate career development planning and address personnel needs, which ultimately will foster a more cohesive Unit spirit. The historical separation of the Unit into two departments is identified as a potential hindrance to scientific exchanges. A proposed reorganization to promote better communication and collaboration among teams is considered beneficial for the institute's overall productivity. Establishing a dedicated Ph.D. program within INEM, allowing students exposure to various team activities and core facilities, coupled with regular mentoring by INEM or IMAGINE researchers, would be considered as a significant step forward. Optimizing administrative support for non-French-speaking researchers is viewed as crucial for enhancing INEM's international visibility and for remaining attractive for the diverse pool of foreign researchers who are welcome in the unit.

Finally, in the recent years INEM has recruited new group leaders either through internal or external calls. The majority of the scientists recruited are already tenured and at the consolidator stage, with little correction for the gender bias existing among group leaders (70% men 30% women). Although this system has allowed the promotion of permanent researchers and appears to be a low-risk approach, young scientists potentially eligible to junior ERCs grants should also benefit from support by a specific program from INEM. Recruiting more Junior level group leaders in the future would ensure the continuous infusion of innovative ideas and technologies crucial for INEM's future resources and productivity.

DETAILED EVALUATION OF THE UNIT

A - CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

The recommendations from the previous report have been largely implemented at the unit level. However, the current frequency of the laboratory council meetings, held twice a year, is deemed inadequate for ensuring effective communication among all staff categories and the leadership at INEM. While improvements have been made in mentoring and monitoring the progress of Ph.D. students, there is a need for a more structured and organized framework specific to INEM. The existing organizational structure, which is heavily dependent on the Ecole Doctorale with the involvement of only two INEM scientists, requires reconsideration.
Although successful in recruiting new teams, the majority of the hires are tenured scientists at the consolidator stage, either internally promoted or from neighboring units. While commendable, this recruitment approach presents a potential risk for the future by creating minimal age gaps among group leaders, hindering the entry of young, emerging talents. These individuals could introduce cutting-edge research topics and technologies crucial for the unit's future resources and productivity, including the pursuit of Junior ERC grants.

B - EVALUATION AREAS

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

Assessment on the scientific objectives of the unit

INEM aims to study cellular functions in pathophysiological contexts, contributing significantly to understand biological processes and addressing health challenges. Research includes identifying molecular pathways, hormones and immune cells in inter-organ communication, as well as exploring disruptions in metabolism and signaling pathways. INEM also investigates how gene expression changes contribute to diseases, being influenced by factors like diet and stress, or during autoimmunity. The unit's scientific objectives are considered outstanding and relevant to current life science challenges.

Assessment on the unit's resources

INEM's resources come from Inserm, CNRS, or UPC providing 1.2 million €/year, and grants secured by research teams, totaling 51 million € from 2017 to 2022 from other sources. State funding covers only 13% of needs, leading to disparities among teams, especially in external funding. Personnel's distribution (300) varies greatly among teams, with a good promotion rate but limited replacement of technical staff. While access to resources is above French standards, improvement of INEM competitiveness, goes with addressing the shortage of permanent ITAs. The overall assessment for this criterion is outstanding.

Assessment on the functioning of the unit

The unit is well-managed, supporting new teams and collaborations, as shown by numerous joined publications. Staff express satisfaction, but improving internal dialogue is necessary. This can be achieved by restructuring departments, more frequent institute meetings and general distribution of PI meeting minutes. Core facilities should be integrated into INEM activities to maximize visibility. Mentoring is excellent, but continued emphasis on PhD and Postdoctorants careers progression is recommended, including more regular progress reports and retreats. The assessment for this criterium is excellent.

1/ The unit has set itself relevant scientific objectives.

Strengths and possibilities linked to the context

INEM teams play a crucial role in integrative pathophysiology, focusing on growth, signaling, metabolism, and immunity. They address pressing health challenges, benefitting from:

Overlapping Areas Fostering Collaboration:
Collaboration is catalyzed by overlapping research areas at INEM. Researchers from different teams find common ground, fostering interdisciplinary collaboration. This approach enriches the research landscape, effectively tackling complex scientific challenges.

Optimal Conditions for Translational Research:
INEM excels in providing researchers with clinical possibilities, emphasizing seamless integration of lab findings into practical patient care. The institute's commitment to translational research is evident in its well-established infrastructure, strong clinical partnerships, and a culture promoting the translation of scientific discoveries into tangible patient benefits, accelerating research findings into clinical practice.

Success in Therapeutics Transition to Clinic:
A notable achievement of INEM is successfully bringing therapeutics from the lab to the clinic. Research teams demonstrate remarkable abilities, advancing findings through various development stages, obtaining regulatory approvals, and effectively introducing novel therapies into clinical settings. This success validates the quality of research at INEM, highlighting significant contributions to medical advancements.

Weaknesses and risks linked to the context

The establishment of a bioinformatic hub is deemed essential for the continued development of the unit. However, the current strategy in place for implementing such hub appears to be insufficient and lack effectiveness. To ensure the success of this crucial initiative, it is imperative to involve various unit personnel actively in the planning and execution processes.

2/ The unit has resources that are suited to its activity profile and research environment and mobilises them.

Strengths and possibilities linked to the context

INEM demonstrates a commendable strength in raising external funding. INEM has been successful in securing several prestigious grants, including those from the ERC and various European funds. INEM's ability to secure industrial contracts and support for startup foundations highlights its proactive approach in diversifying funding sources, ensuring financial stability, and fostering innovative research initiatives.

State-of-the-Art Core Facilities: The Structure Federative of Recherche facilities at INEM play a pivotal role in providing technological access to all teams. This infrastructure ensures that researchers have state-of-the-art tools and resources at their disposal, promoting cutting-edge experimentation.

Well-Organized Access to Clinical Samples: INEM boasts a well-organized system for accessing clinical samples. This streamlined process facilitates researchers' access to key clinical material, enabling them to conduct studies with relevance to human health and enhancing the translational potential of the research conducted at INEM.

Collaborations with neighboring Institutes: INEM has strong collaborations with neighboring research institutions, including IHU Imagine and the Pasteur Institute. These collaborations create a collaborative ecosystem, fostering the exchange of ideas, expertise, and resources. Such partnerships contribute to a broader research perspective, allowing researchers at INEM to benefit from synergies and shared knowledge across institutes.

Weaknesses and risks linked to the context

The INEM research institute faces a critical need for the renewal of permanent technical staff, primarily stemming from the non-replacement policy enforced by the governing bodies. The absence of a systematic approach to replenishing technical positions jeopardizes the institute's operational efficiency and the continuity of essential functions performed by technical staff.

The INEM research institute currently faces a notable gap in support from the AP-HP (Assistance Publique - Hôpitaux de Paris) hospital which is not a tutelle. Specifically, critical situations such as the provision of laboratory technicians and the facilitation of robust clinical collaborative networks could be improved by an increase partnership.

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

Strengths and possibilities linked to the context

No strength identified since INEM has to comply with these regulations.

Weaknesses and risks linked to the context

INEM faces weaknesses requiring interventions for fortification and a more inclusive research environment:
1. **APs Reorganization:** The current "assistants de prevention" task force needs complete reorganization by redefining roles, improving workflows, and enhancing preventive actions.

2. **Data Management Plan:** While commendable for implementing Labguru, INEM lacks a comprehensive DMP, posing vulnerability. Establishing a centralized data center and archiving mechanisms is vital for data accessibility and preservation.

4. **Improvement of Intranet and Website:** Enhancement in design and content is essential for effective internal communication and presenting INEM externally.

5. **Gender Equality Committee:** INEM's gender equality efforts are commendable, but further action is needed. A measurable short-term and long-term strategy should be outlined to improve gender representation among group leaders in particular.

6. **Implementation of an Actualized "Réglement Intérieur":** Implementing a comprehensive set of updated regulations and policies is necessary for clarity, transparency, and structured operations.

7. **Communication Within the Institute:** Enhancing communication through PI meeting minutes and increased Laboratory Council frequency, with diverse representation, will contribute to transparent decision-making.

8. **Scientific Integrity Referent:** The absence of a designated scientific integrity referent is a concern.

EVALUATION AREA 2: ATTRACTIVENESS

Assessment on the attractiveness of the unit

INEM's global reputation attracts international talent, with a third of its personnel from outside France. 40% of its PIs are foreign nationals, highlighting its appeal to top researchers worldwide. The institute actively enhances its international standing through strategic initiatives, including weekly seminars and visits by professors from various countries. INEM's commitment to excellence is evident in funding schemes and substantial investments in cutting-edge technology, reinforcing its international competitiveness. The assessment for this criterion is outstanding.

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

1/ The unit has an attractive scientific reputation and is part of the European research area.
INEM's attractiveness as a research institute is undoubtedly underscored by its researchers' extensive engagement on the national and international stage. With over 500 presentations at prestigious conferences and universities, INEM researchers consistently contribute to the global scientific dialogue. Moreover, their involvement in organizing international meetings, including notable gatherings such as the "TOR de France" and EMBO meetings, highlights the institute's commitment to fostering collaboration and knowledge exchange. The biennial hosting of an international symposium further enhances INEM's appeal, offering a platform to showcase its main research interests. The diverse thematic focus of these symposia reflects the institute's scientific community's breadth and depth. Notably, the symposium celebrating the reunification of all INEM teams in 2020 marked a significant milestone in the institute's history.

The initiation of the Association of ERC Grantees (AERG) web conferences, featuring renowned speakers like Uğur Şahin, CEO of BioNTech, adds another dimension to INEM's attractiveness. With nearly 900 participants, this initiative demonstrates the institute's ability to bring together a broad audience for cutting-edge discussions. INEM researchers' involvement in editorial responsibilities, peer review activities, and participation in scientific councils further contributes to the institute's standing. These engagements highlight the researchers' recognition within the broader scientific community and their commitment to advancing knowledge beyond the institute's borders.

The numerous prestigious awards received by INEM researchers, totaling 53 to date, exemplify the high regard their contributions receive. Notable achievements, such as the "Grand Prix de Medecine de la Ville de Paris" and the "Einstein Visiting Professor" award, showcase the caliber of talent within INEM.
In summary, INEM's attractiveness is evident in its researchers' prolific international engagements, symposium organization, and the institute's ability to draw renowned speakers.

2/ The unit is attractive because for the quality of its staff support policy.
INEM has been able to recruit a relatively high number young/consolidator principal Investigators, showcasing the institute's robust standing in the global scientific community. Bolstered by exceptional scientific activities, cutting-edge technology platforms, and its affiliation with the internationally renowned Necker Hospital, INEM has become a sought-after hub for emerging researchers. Crucially, the institute provides substantial support to incoming PIs through the backing of the "Fondation Recherche Necker Enfants Malades" (FRNEM) and a shared budget. This support manifests in a generous welcome package empowering newly arrived researchers to delve into their scientific pursuits and contribute to the continued success of INEM. INEM's international allure is further emphasized by its recognition as a highly desirable destination for foreign researchers, post-docs, and Ph.D. students.

3/ The unit is attractive through its success in competitive calls for projects.
INEM's attractiveness is heightened by its robust financial support, reflective of the institute's successful acquisition of various grants and contracts. Between 2017 and 2022, INEM demonstrated a remarkable capability to double its external funding, securing an impressive total of 450 contracts amounting to approximately 51 million euros. This substantial financial backing is derived from diverse sources, showcasing the institute's adeptness in obtaining national grants, including 88 ANR grants. The upward trajectory in funding is evident in the steady increase over the years, with for 2022 alone, the obtention of 22 ANR grants. A noteworthy achievement in this financial landscape is the successful funding secured by Guillaume Canaud for the COSY project (Curing Dysharmonic Hypergrowth Syndromes) through RHU grant of 2.5 million euros, a collaboration with the Necker Enfants Malades hospital. The institute's prowess is further underscored by its success in securing prestigious grants from the European Research Council (ERC). INEM's financial success, marked by its adeptness in securing diverse grants and contracts, not only sustains its research activities but also serves as a testament to the institute's attractiveness in the competitive research landscape.

4/ The unit is attractive for the quality of its major equipment and technical skills.
INEM stands out as an attractive research institute due to its exceptional technological infrastructure and commitment to advancing research capabilities. The Necker campus, in collaboration with the Imagine Institute, benefits from cutting-edge platforms within the "Structure Fédérative de Recherche (SFR) Necker", showcasing a shared commitment to excellence. The institute actively contributes to this collaborative structure through financial support for equipment acquisition, salaries, and the development of new platforms, directly contributing to 28% of the total investment of 2.2 million euros between 2017 and 2022. Notable acquisitions include equipment for histology, cytometry, cell imaging, proteomics, neurobehavioral studies, and genome editing. INEM's systematic approach ensures continuous improvements and additions to its technological capabilities, fostering an environment conducive to cutting-edge research.

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

No weaknesses identified.

EVALUATION AREA 3: SCIENTIFIC PRODUCTION

Assessment on the scientific production of the unit

The 21 teams of INEM have published a total of 1620 articles over the period of 2017-2022. A great number of them were in high-profile journals, which underscores the high standard of research produced at INEM. It is worth noting that a significant number of publications were the result of collaborative work among several INEM teams, highlighting the dynamic and collaborative nature of the institute. The assessment for this criterium is 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/ The scientific production of the unit meets quality criteria.
The number and the quality of the scientific publications of the unit meets excellence and is distributed throughout the different teams of INEM.

2/ The unit's scientific production is proportionate to its research potential and properly shared out between its personnel.
INEM has a well-defined publication approach across all teams, fostering collaboration, knowledge dissemination, and active participation of team members at various career stages, as seen from:

Authorship Inclusivity: The strategy acknowledges the importance of recognizing the contributions of all team members. The inclusion of PhD and Post-doctorants as first authors on papers related to their projects, and the flexibility for junior scientists to sign as first or last authors based on their involvement, demonstrates a commitment to acknowledging individual efforts.

Collaborative Environment: The practice of listing all team members who contributed to a project as co-authors reflects a collaborative and inclusive environment.

Structured Data Sharing: The regular lab meetings, where experimental data are presented by everyone involved in the work, contribute to a structured and open data-sharing culture. Additionally, the annual presentations to the departmental lab meeting provide a broader platform for PhD students and Post-doctorants to showcase their work and receive feedback.

Encouragement of Presentation Skills: The encouragement of young scientists to present oral communications or posters at national and international conferences reflects a proactive approach to developing presentation skills and increasing visibility.

In conclusion, the publication strategy at INEM is commendable for its inclusive and collaborative approach, structured data-sharing practices, and proactive encouragement of presentation skills among young scientists.

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.

INEM demonstrates a commitment to research integrity and ethical standards
Traceability and Reproducibility:
- Implementation of a mandatory electronic notebook (Labguru) approved by Inserm.
- Use of Labguru to link and save all relevant data, including storage location, backup procedures, protocols, and metadata.

- Open sharing of research data with unique identifiers (DOI) and rich metadata under a Creative Commons license for persistent findability and reusability.

Patients' Consent and GDPR Compliance:
- Involvement of human blood samples sourced from healthy donors or consenting patients.
- Adherence to European GDPR regulations and French Méthodologie de Référence MR-004.
- Provision of patient rights, including access to study information, withdrawal options, and control over participation through data processing objection forms on Expert Centers' websites.

Ethics in experimentation:
- Compliance with French and European regulations and directives, following the 3R rules.
- Authorization of research projects by the Ministry of Research based on recommendations from the Ethics Committee of University Paris Cité (CEEA34).
- Dedicated local reading committee and interaction with the "Animal Well-being" committee to monitor and ensure ethical standards throughout the projects.
- Active participation of INEM scientists in key committees, including the Ethics Committee (CEEA34), Reading Committee, and Animal Well-being Committee.

Open Access Publication Strategy:
- Emphasis on publishing in open access journals to widen accessibility and transparency of research.
- Commitment to making research findings available to a broader audience, aligning with principles of transparency and knowledge dissemination.

In summary, INEM's adherence to traceability, patient consent, and open access publication practices underscores its commitment to research integrity and ethical standards. The unit's multifaceted approach ensures transparency, reproducibility, and responsible conduct in research activities.

Strengths for these items.
- Outstanding scientific productivity
- Full respect of authors contribution
- Ph.D students publish as first authors
- Full compliance with scientific integrity and ethics rules

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

A INEM referent for Scientific integrity needs to be identified at INEM and specific integrity regulations need to be mentioned in a novel "réglement intérieur". (See also comments in point 3 "The unit's practices….").

EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

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

INEM's proactive engagement with strategic collaborations with industry, income generation, consultancy services, and the creation of start-ups collectively underscore the institute's outstanding impact on the cultural, economic, and social landscapes. These initiatives reflect a dynamic and forward-thinking approach to research with tangible contributions to societal and economic advancements. The institute's outreach extends beyond traditional academic boundaries, contributing to a broader impact on healthcare and research communities.
The assessment for this criterium is outstanding.

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

1/ The unit stands out for the quality and the amount of its interactions with the non-academic world.
INEM stands out significantly through its remarkable contributions to the economic and clinical world.

Strategic Industrial Collaborations:
Robust collaborations exist with major pharmaceutical companies, including Novartis, Moderna or Janssen. The signature of 55 industrial collaborative contracts between 2017 and 2022, secured significant income through industrial collaborations, exemplified by the Pontoglio/Terzi's teams obtaining a 4 M€ contract with Janssen and demonstrating their ability to translate research outcomes into tangible economic benefits for the institute.

CIFRE PhD Programs:
Many CIFRE PhD programs with various pharmaceutical companies, including Xentech, Sanofi, Enyo, Zion Pharma, Rarecells, and Alehos, have facilitated the integration of industrial perspectives into research, fostering innovation, and enhancing the employability of PhD candidates.

Consultancy Services:
The active involvement of INEM researchers in consultancy services to companies, offering expertise in clinical trials, novel therapeutics, and technological developments, shows the institute's impact beyond traditional research boundaries.

Entrepreneurial Initiatives:
Establishing two start-ups, Rarecell and AfXOS, within the past six years, demonstrate the entrepreneurial spirit and innovative drive of INEM's researchers.

2/ The unit develops products for the cultural, economic and social world.
The development of the FDA-approved drug Alpelisib for overgrowth syndrome, thanks to the close collaboration between Canaud's team and Novartis is a perfect example of the capacity of INEM to translate its research in products for the economical world. In addition, INEM researchers actively engage in meaningful collaborations beyond academia, fostering connections with patient associations and supporting foundations including "Association Vaincre la Mucoviscidose", "Association pour l'Information et la Recherche sur les Maladies Rénales Génétiques," "Association Sclérose Tubéreuse de Bourreville," and "Federation Française de Diabetiques." INEM researchers are also involved in supporting foundations that promote research and innovation. These initiatives reflect INEM's commitment to societal engagement, patient-centric research, and collaboration with organizations dedicated to advancing medical knowledge and supporting research and innovation.

3/ The unit shares its knowledge with the general public and takes part in debates in society.
INEM researchers actively engage in science communication and outreach efforts, reaching diverse audiences. Key points include:

Media Presence:
Researchers regularly share their findings through talks, interviews, and media appearances on national and international platforms, including newspapers, TV, and radio.

Participation in dissemination events such as "Bar des Sciences", "Fête de la Science," and programs at the "Cité des sciences et de l'industrie."

COVID-19 Pandemic Contribution:
Notable efforts during the COVID-19 pandemic, including the creation of a video titled "Vaccination for beginners" by Claude-Agnès Reynaud, Aleksander Edelman, and Jean-Claude Weill. The video, addressing fears surrounding RNA vaccination, has garnered thousands of views on YouTube.

Scientific Interest Promotion:
Dedication to promoting scientific interest among students and children through participation in programs that allow young students to attend lessons and spend time in the lab, fostering an early discovery of the world of research.

These activities underscore the commitment of INEM researchers to science communication, education, and addressing public concerns, contributing to a broader understanding of scientific advancements and fostering interest in research among diverse audiences.

Strengths for the 3 items:

• The strong connections with industry which enables collaborations and a significant source of income for the teams.
• The high number of filed patents (55 for the 2017-2022 period), which confirms INEM's strong focus on innovation and intellectual property protection.
• The success of INEM researchers in sharing their findings with the public and engaging with patient associations
• The strong involvement in school teaching programs, demonstrating a commitment to the development of the next generation of researchers and scientists.

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

The identity and the recognition of the INEM institute currently lack clarity, extending to the institute's logo and overall image. There is a need to enhance the distinctiveness of INEM compared to other research institutes. An effective strategy could involve a concerted effort to refine the institute's visual identity and emphasize its unique research interests.

ANALYSIS OF THE UNIT'S TRAJECTORY

INEM's trajectory shows remarkable strengths in scientific excellence, global reputation, financial sustainability, and research impact. While acknowledging these achievements, the unit is actively addressing identified areas for improvement to ensure ongoing success, adaptability, and inclusivity. The commitment to fostering an attractive environment for researchers, coupled with a strategic approach to organizational and communication enhancements, positions INEM for continued excellence in the dynamic field of integrative pathophysiology.

1. **Scientific Excellence and Focus:**
· INEM's research focus on cellular functions in pathophysiological contexts, including growth, signaling, metabolism, and immunity, positions it at the forefront of integrative pathophysiology.
· Exceptional contributions to understanding molecular pathways, hormones, and immune cells' roles in inter-organ communication.
· Active involvement in translational research, evidenced by successful FDA-approved therapies originating from INEM's research.

2. **Global Reputation and International Engagement:**
· INEM excels in international visibility with a third of its personnel being international, and 40% of its Principal Investigators being foreign nationals.
· Participation in international conferences, hosting symposia, and initiating web conferences, showcasing a commitment to global scientific dialogue.
· Recognition through awards and achievements, further solidifying INEM's position in physiopathology and immunology research.

3. **Financial Sustainability and Resource Access:**
· Successful grant acquisition, securing significant funding from diverse sources, including ANR, ERC, and industrial contracts.
· State-of-the-art SFR core facilities and well-organized access to clinical samples contribute to cutting-edge research capabilities.
· Strong collaborations with neighboring institutes enhance research perspectives and shared knowledge.
·
4. **Research Output and Impact:**
· INEM consistently excels in scientific production, publishing original research articles in esteemed journals.
· Actively addressing recommendations by enhancing workforce, recruiting promising team leaders, and fostering collaborations.
· Active involvement of clinicians in research teams and FDA approval of therapies highlight the unit's impactful translational research.
·
5. **Attractive Environment for Researchers:**
· Attraction of talented researchers, evidenced by the recruitment of new Principal Investigators and a diverse workforce.
· Generous support for incoming PIs through the FRNEM and shared budget, empowering researchers to contribute significantly.

Areas for Improvement:

1. **Organizational Adaptations and Communication:**
· A need for increased transparency and top-down communication during the ongoing transformation, especially concerning permanent staff and graduate students.
· Historical separation into two departments identified as a potential hindrance to scientific exchanges; recommended reorganization for better collaboration.
- Visibility of INEM as a research brand somewhat blended in the Necker environment.

2. **Gender Diversity and Recruitment Strategy:**
· Acknowledgment of gender bias among group leaders.
· Potential risks associated with the current recruitment strategy, with a majority of scientists recruited being tenured and at the consolidator stage, with the need the need for a balanced approach to recruiting younger scientists to ensure continuous innovation.

3. **Administrative and Intranet Improvements:**
· Obsolete "réglement intérieur"
· Need for improved bottom-to-top communication

4. **Mentorship Programs and International Support:**
· Need to increase mentorship programs and establish PhD and Postdoctorants committees for professional development.
· Optimization of administrative support for non-French-speaking researchers.

5. **Scientific Integrity and Data Management:**
· Need of Scientific Integrity Referent.
· Need the Implementation of a well-defined data management plan and centralized data center.

RECOMMENDATIONS TO THE UNIT

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

Update the "réglement intérieur" to establish transparency and preventing ambiguity about INEM policies.

Enhance communication through minutes from PI meetings, increased Laboratory Council frequency, and more involvement of diverse personnel in the decision-making process.

Reevaluate the departmental structure, considering a more dynamic organization to promote innovation and increased exchanges among laboratories.

Introduce an INEM Ph.D. program with annual individual dialogs between students and supervisors outside the ED to enhance academic success and integration.

Boost scientific exchanges by holding a yearly scientific retreat, also involving SFR core facilities.

Initiate a comprehensive reorganization of assistant prevention's role, improving responsibilities, workflows, and preventive measures.

Implement a bioinformatic hub by actively involving dedicated unit personnel, recruiting additional computational biologists, and defining a clear strategy for effective collaboration among users.

Implement a comprehensive data management plan and establish a centralized data center for secure, compliant research data handling.

Invest in the Intranet and website for improved internal communication and external presentation.

Appoint a Scientific Integrity Referent to oversee and promote ethical standards in research activities at INEM.

Recommendations regarding the Evaluation Area 2: Attractiveness

1. A general reflection about INEM research specificity on the Necker site and a branding strategy to improve INEM visibility and name recognition should be undertaken to increase Institute cohesion and actively promote INEM on the international stage. This may be achieved through the organization of international conferences focusing on INEM specifics, collaborations and showcasing the institute's clinical achievements or research contributions through various global platforms. In addition, INEM should invest more in a Public Relations Office, led by the recently hired Communication Officer, which would implement a more aggressive media coverage policy, beyond the currently very successful X (Twitter) account, to other social media, issuing press releases for national newspapers and organizing appearances, interviews in science-related TV shows.

2. Increase the recruitment of talented junior group leaders (<7y after Ph.D) from diverse specialty and international backgrounds.

3. In line with its broad focus and translational activities, INEM should consider the establishment of an international Ph.D. program. This program could attract talented students from around the world, positioning INEM as a hub for cutting-edge life science research and clinical transfer on the international stage.

Recommendations regarding Evaluation Area 3: Scientific Production

No recommendation required for this area.

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

1. Considering the association with the renowned Necker Hospital, leveraging the hospital's positive image could be beneficial. Drawing inspiration from the Necker Hospital's successful branding strategies may provide insights into enhancing the visibility and distinctiveness of INEM. Establishing a clear and compelling institute identity will not only strengthen its presence but also facilitate a better understanding of its research objectives among various stakeholders.

TEAM-BY-TEAM OR THEME ASSESSMENT

Part to be duplicated for each team according to the organization of the unit, be sure to use the nomenclature used by the unit (teams, axes, themes, etc.).

Team 1: Genome plasticity and infections

Name of the supervisor: Laurence Arbibe

THEMES OF THE TEAM

The team comprises two subgroups, one led by L. Arbibe (DR) and the other one by D. Skurnik (PU/PH) heavily involved in clinical research. The team's research focuses on four main areas: (i) identifying epigenetic regulators that maintain intestinal tolerance and exploring their potential therapeutic applications in the treatment of inflammatory bowel disease (IBD). (ii) investigating bacterial mechanisms that promote genomic instability in the gut, with a particular focus on genotoxins released by enterobacteria (ii!) identifying bacterial factors that interact with the inflammatory and immune systems of the host, and (iv) developing promising novel immunotherapy approaches to prevent or treat bacterial infections, including those caused by multidrug-resistant and pan-resistant strains.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

It was stated at the time of the previous evaluation that further funding would be important to improve competitive position (ERC for example would be an obvious choice). It was also suggested that the team should collaborate more with other INEM teams, and that work on enterobacterial genotoxins should be more competitive. All these points are still relevant. On the other hand, the team did take into account the need to grow with the arrival of David Skurnik.

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

Staff Total	14
Staff scientists	2
MCU/PU/PH	4
Technicians and engineers	2 permanents + 2
Post-doctorants	2
Ph.D students	2

EVALUATION

Overall assessment of the team

The team is excellent. The objectives of Team 1 are well-defined for their innovative work on HP1 and vaccination/immunotherapy, with promising prospects for both fundamental and applied research. The team's recent publications in Nature Communication and EBioMedicine have validated their research strategies and opened up a new area of investigation. The team has been successful in securing funding so far.

Strengths and possibilities linked to the context

Good to very good scientific production.
Excellent contribution to new knowledge.

Innovative research program.
Partnerships with industry have been in place in the past, and would have to be further developed.

Weaknesses and risks linked to the context

More funds have to be secured for the future and from diverse sources.
European research programs should be fostered.
Dissemination to the public does not seem to be a priority of the team.
Visibility of the team leader could be improved.

Analysis of the team's trajectory

Team 1's objectives for the upcoming years are precisely defined and thoroughly described. Research axis 1 builds on excellent work published by Laurence Arbibe in Nat Com in 2022 on the role of HP1 in recurrent inflammation of the rectum and colon during ulcerative colitis. This project is innovative and has great potential beyond IBD. Research axis 2 is less convincing. The release of this genotoxin and bacterial products may be thought to play a role in inflammation or even cancer, but this work is not as competitive and promising as axis 1. Research axis 3: given that there is no genetic definition of AIECs, it is questionable whether a mutagenesis approach should be used to search for virulence factors. This TnSeq approach makes much more sense with *E. coli* strains expressing the K1 capsule and responsible for meningitis. The initial results of this work have been published in EBioMedicine and are the starting point for work on the PNAG. Research axis 4 on the discovery of new vaccine targets and new immunotherapy approaches is very promising and has already produced results that were published in PLoSPathogens at the end of last year, when the HCERES report had already been submitted. This work is a direct result of the expertise acquired by David Skunik in the field and his high interest in clinical research with industrial development potential.

RECOMMENDATIONS TO THE TEAM

Given the potential of the team's work in epigenetics, the group led by Laurence Arbibe should focus more on this subject and spend less time on the enterobacteria genotoxin project, which is much less competitive, except for using genotoxins in general as actors of epigenetic modification. Research funds to support the planned program are in part secured but more funds from diverse origins will have to be secured. The committee encourages the team, and David Skurnik in particular, to continue to actively explore industrial partnerships that align with their research strategy.

Team 2: Normal and pathological lymphoid differentiation

Name of the supervisor: Vahid Asnafi & Elizabeth Makintyre

THEMES OF THE TEAM

The team has a long-term expertise in the cellular and molecular events implicated in lymphoid development, early TCR gene recombination and lymphoid malignancies. The recent scientific production is notably related to various oncogenic processes at work in T cell malignancies, notably the alterations of PRC2, MYB, TAL1, BCL11b, PHF6, and the involvement of T-cell recombination circles into oncogenesis for which both molecular aspects and clinical implications are studied, capitalizing on an extensive collection of annotated leukemia/lymphoma samples. The projects are at the interface between basic research and clinical haematology, with direct implications for the molecular diagnosis of immature T cell leukemia or T-cell lymphoma and the prediction of their response to therapy.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The move to the new building in 2018 did not affect the internal organization or the scientific production of the team. The team incorporated a new permanent Inserm CRCN researcher in 2022. However, the interaction and collaborations with other teams of the unit did not improve significantly during the last term.

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

Staff Total	**22**
Staff scientists	1
MCU/PU/PH	2 PU-PH, 4 MCU-PH
Technicians and engineers	3 permanents + 6
Post-docs	1
Ph.D students	5

EVALUATION

Overall assessment of the team

The team is outstanding by successfully combining regular, focused but nevertheless diversified scientific productions in high impact journals, together with a strong involvement into valorisation and transfer to diagnosis and clinical practice. The team participates and leads several national and/or European networks and clinical collaborative groups. The team is involved in implementation science, strengthening the links between academia, manufacturers and regulators. The team had a clear commitment to mentoring young clinicians and scientists.

Strengths and possibilities linked to the context

The team successfully combines basic and clinical research, with important scientific discoveries focusing on the mechanisms of normal function and malignant transformation of T cells. Importantly, the findings of these publications have been translated into improvement in the diagnosis and treatment of T-ALL patients.
The involvement in teaching and training of the next generation of hematologists is very significant.
The team has strong interactions with the non-academic world, including national lymphoma networks such as the Carnot Institute 'Calym' dedicated to lymphoma and other scientific committees (Fondation de France, FRM).

Weaknesses and risks linked to the context

Potential changes into the organization of clinical haematology departments throughout Paris University hospitals are planned (although yet not with a detailed roadmap) and may change the organization of work in the unit, at the interface between research and the clinical laboratory. This might include the move of the team to the new Institute of hematology at Cochin in 2026-2027, which will divide academic and clinical activities, which are currently in the same space. However, these changes are well anticipated by the Team which seems willing to adapt and contribute to the "meta" evolution.

Analysis of the team's trajectory

The scientific production of the team is quite regular, with successful Interactions/synergy between the academic lab and the hospital. The team also has an excellent international reputation and has everything it takes to maintain it during the next 5 years in terms of projects, personnel and funding.

RECOMMENDATIONS TO THE TEAM

The team should certainly stay on the scientific course it has set, and expand their research projects focused on lymphoma during the next term. The team should also be ready to take advantage of and support developments in the "haematology context" in Paris. The team may consider expanding their network of collaborators, including more international (outside Europe) researchers to increase their visibility in the context of hematological malignancies. It would be very valuable if the team could apply their expertise on European cooperative actions to strengthen the relationships between researchers and patient advocates in France.

Team 3 : Immunoregulation and Immunopathology

Name of the supervisor: Lucienne Chatenoud & Maria Leite de Moraes

THEMES OF THE TEAM

Two main themes:

13. Pathogenic and regulatory immune mechanisms in autoimmunity and devise of strategies to induce/restore immune tolerance.

- - Clinical use of CD3 monoclonal antibodies to prevent/ treat established autoimmune diabetes (T1D).
- - Genetic factors impacting disease progression in non-obese diabetic (NOD) mice (generation by selective breeding of two sub-strains of NOD mice).

2. Ontogeny, differentiation and functional heterogeneity of invariant Natural Killer T (Inkt).

  - – immunoregulatory role of Inkt cells in relevant pathological conditions including experimental allergic asthma focusing on severe asthma.
  - – immunoregulatory role of Innate Like T (ILT) cells in allergy, in particular Inkt and γδ T cells roles in the severity of the pathology.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

As stated in the self-evaluation document, the previous report underlined outstanding scientific achievements and no corrective actions needed. The other recommendations, in particular on recruitment for new teams don't apply here.

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

Staff Total	11
Staff scientists	1
MCU/PU/PH	4
Technicians and engineers	3 permanents + 1
Postdoctorants	2
Ph.D students	1

EVALUATION

Overall assessment of the team

The scientific production of the team is very good. It encompasses two distinct areas, autoimmunity and allergy. Both areas fruitfully associate fundamental and clinical research, with on one side development of new relevant experimental models, on the other, construction of important cohorts. As an example, the team has fruitfully reached its long-standing goal of translating into practice fundamental findings, especially through recent approval of a new drug to prevent Type 1 diabetes.

Strengths and possibilities linked to the context

Attractiveness: A possible concern relates to a low attractiveness of a group that will split and conclude research activities in the near future.

The scientific production of the team encompasses two distinct areas, autoimmunity and allergy.

First, this later period enabled the team to achieve a new therapeutic avenue in autoimmune diabetes: ultimately, a randomized placebo-controlled study of "at risk" children from the families of T1D patients conducted by the team showed that a short 14-day CD3 antibody course was followed by a three year-delay in insulin dependency development. These results supported approval of the CD3 antibody Teplizumab for prevention of T1D by the Food and Drug Administration last November 2022.
Another line of research relates to investigating genetic factors involved in T1D induction in NOD mice. In the past years, the team has acquired new expertise in genetic studies and thanks to international collaboration discovered new mutations that accelerate disease in novel genes not previously identified in T1D.
Specifically, the team undertook a nondirected mutagenesis program with the chemical mutagen N-ethyl-N-nitrosourea (ENU) and then used automated meiotic mapping to identify *de novo* modulators of autoimmune diabetes. This analysis of a small number of genetic changes in each pedigree permits to elicit causation of specific mutations. Seven mutations that accelerated T1D development and five that delayed or suppressed T1D were identified by the team. Eleven mutations affected genes not previously known to influence T1D.

Second, the team made use of experimental models of allergic asthma to elicit implication of innate-like T (ILT) cells, namely iNKT and γδ T cells, in the severity of the pathology. Furthermore, the team started a project to study several factors regulating severe asthma in children with collection of different blood, bronchoalveolar lavage, lung biopsy, saliva, and found an association between percentages of MAIT cells and severe asthmatic exacerbation. These analyses are a first step to better identify the T cell populations of interest and their location (blood, BAL) in order to specifically sort them and perform more advanced studies such as single cell RNA sequencing. The team is also studying a cohort of 200 children allergic to cow's milk to determine whether ILT contributes to the allergic responses observed in these patients, in the aim to identify tolerant and non-tolerant patients.

Inclusion of the team in society is important, considering its contribution to FDA approval of the CD3 antibodies treatment for TD1. The team also shares its knowledge with the general public, takes part in debates in society and is financed by patients' associations where public reports of the ongoing research are provided.

Weaknesses and risks linked to the context

Not relevant, as the team will split in two parts due to retirement of one supervisor

Analysis of the team's trajectory

As said previously, the team is going to be closed with one PI who will retire (she will continue with a funded-project up to retirement) and the other supervisor (MLDM) joining team 4.

RECOMMENDATIONS TO THE TEAM

Not fully relevant. However, it must be noted that one part of the team (LC) will need to find some lab space within another team up to retirement to finish the NIH-funded project (genetics of the NOD mice) prior to retirement. The other part (MLDM) will continue research by joining team 4.

Team 4 : Immunity in Health and Disease

Name of the supervisor: Simon Fillatreau

THEMES OF THE TEAM

The team of Simon Fillatreau followed an outstanding path unravelling the biology of regulatory B cells (BREG), plasma cells and regulatory T lymphocytes (TREG). The future will also benefit from the arrival of outstanding clinicians and investigators who will broadens the area of research, although the team will remain coherent and focused on immunoregulation. Major themes are about the function and the therapeutic manipulation of BREG and TREG cells, with translational research about their potential usage for immunotherapy.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Most of the few recommendations made have been followed.

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

Staff Total	**12**
Staff scientists	1 CR Inserm
MCU/PU/PH	1 PU-PH, 1 MCU-PH
Technicians and engineers	1 permanent + 3
Post-docs	3
Ph.D students	2

EVALUATION

Overall assessment of the team

The team made a number of outstanding contributions to the field, in particular detailing the regulatory functions of BREG cells, natural regulatory plasma cells, TREGS and exploring the molecular determinants MZ versus follicular B cell differentiation. The team is internationally recognized for these seminal discoveries and the most recent data from the team are highly promising. The programme is highly innovative, clearly argued and obviously feasible given the reputation of the investigators and their proven ability to attract funding (in particular ERC, Horizon Europe, ANR and others...).

Strengths and possibilities linked to the context

The team strategy and organization in three groups is coherent and strengthened by the integration of new investigators broadening the expertise about immunomodulation and regulatory lymphocytes, as well as on innate immune cell subsets and their role in autoimmune and other immune-mediated diseases. Synergy between these groups can be expected since they all address issues connected with self-tolerance and regulation of adaptive immunity, although in various models and physiological or clinical settings. The team strong has strong and highly valuable collaboration with the clinical departments of the Necker Hospital, in particular nephrology, which can favor translational research.

The research projects can also be expected to yield direct applications for therapy.

Weaknesses and risks linked to the context

No major weakness.
Since the 3 groups are addressing different aspects of immunopathology, from auto-immunity, to allergy and transplantation immunology, ensuring that the team remains focused along the contract could however be a challenge.

Analysis of the team's trajectory

Simon Fillatreau's team followed an outstanding path, in particular unravelling the biology of regulatory B cells, natural regulatory plasma cells and connecting TREG function with TCR affinity. Those discoveries paved the way to important clinical translation with innovative cellular therapies in autoimmune diseases. The future team will now also integrate other outstanding researchers and clinicians coming from other teams from the Necker campus (Julien Zuber, Maria Leite de Moraes and Peter van Endert), thus broadening the scope of research but remaining very coherent and focused on immunoregulation. A major theme will remain regulatory lymphocytes (both BREG and TREG cells), basic research on their function and translational research on their potential manipulation for immunotherapy of immune-mediated inflammatory diseases (IMIDs). The remainder of the research programme also aims at exploring original immunotherapy and cell therapy strategies adapted to transplantation, in particular using engineered Tregs cells.

RECOMMENDATIONS TO THE TEAM

The scientific objectives should remain focused along the next contract with the “task force” converging towards the most innovative scientific aims.

Team 5: PRL/GH pathophysiology: translational approaches

Name of the supervisor: Vincent Goffin

THEMES OF THE TEAM

The team's research activity relates on the field of Onco-Endocrinology and focuses on breast and prostate cancers and the molecular and cellular pathways underlying therapeutic resistance.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team has taken into consideration the recommendations of the previous HCERES committee. The generation of a prospective biocollection of human prostate cancer specimens, and the cognate development of organoids from fresh tissue (starting), validate the strategic recruitment of urologists to address one of their recommendations ("Extending findings on prostate cancer stem cells from murine models to human samples would greatly strengthen their clinical impact").
A weakness raised by the HCERES committee ("No commercial exploitation of the patents is reported") no longer applies as the two patents of A. Hamaï have been licensed by a start-up.
Finally, according to a recommendation about our scientific policy ("The scientific strategy of the team is very good but the team needs to carefully focus research activity") the team decided to close some projects and focus the next period on three main core projects only. This focused research fulfils the recommendation of the previous HCERES committee.

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

Staff Total	**15**
Staff scientists	5
MCU/PU/PH	2
Technicians and engineers	2 permanents
Post-docs	1
Ph.D students	5

EVALUATION

Overall assessment of the team

The team studies prostate and breast cancer. Its scientific output is impressive, attracting high-quality recruits. The team actively engages in training through research with eight PhD students and eight researchers with HDR. The team's interaction with the clinic is outstanding. Extensive connections with the industrial world include CIFRE PhD theses and collaboration partnerships. In the competitive prostate cancer research field, the team provides unique insights, leveraging deep knowledge of prolactin. Notably, their focus extends beyond cancer to benign overgrowth, a still underexplored area.

Strengths and possibilities linked to the context

During the past six years, the team has co-authored 76 papers, of which 20 original articles and 13 review articles were coordinated by team members (first/co-first/last/co-last/corresponding authorship). Few publications appear in high ranked journals (as first or last authors in Nature Chemistry, Autophagy, Cancer Research). The large number of collaborative papers highlights the involvement of the team in multi-institution networks through France and abroad.
Dissemination to the general public mainly concerns schoolchildren sensitization to research professions by team researchers, and general population sensitization to various healthcare issues, including cancer prevention, diagnosis and therapeutic options, by clinicians.

The ability to integrate basic and clinical science and to recruit new permanent staff during the last few years is a particular strength. During the past contract, the team recruited three Inserm/CNRS researchers, three clinicians, and one tenure technician, leading to a staff of up to eleven tenure people. Since 2017, the team has attracted seven PhD students. All PhD students published at least one first-author original paper on their research topic.

The Team is co-inventor on three patent families, two of which are licenced by a start-up.

Weaknesses and risks linked to the context

Most of the publications in the highest ranked journals are in collaboration.
The visibility of the team can be ameliorated by increasing the participation to National and International Meetings.
The team currently has no European/international grants.
The team management by V. Goffin includes yearly meetings with each lab member individually. Global strategic decisions for the lab are discussed at bi-yearly COMEX meetings gathering staff members. The frequency of these meetings could be improved.

Analysis of the team's trajectory

The team has taken into consideration the recommendations of the previous Hcéres committee. The generation of a prospective biocollection of human prostate cancer specimens, and the cognate development of organoids from fresh tissue (starting), validate the strategic recruitment of urologists to address one of their recommendations ("Extending findings on prostate cancer stem cells from murine models to human samples would greatly strengthen their clinical impact").
The scientific program appears strong and robust and can generate original data with competitiveness at an international level. The team has discontinued some research projects that were the objectives of the previous Hcéres evaluation and now focuses on three well-defined research axes with long-term goals, and often based on solid and recognized research in the past.
These three projects coherently fit with the team's core objective to address mechanisms of progression and resistance to treatment of hormone-dependent tumors that share several features and respond to similar rules.

RECOMMENDATIONS TO THE TEAM

Aim for more high impact publications including members of the team as first/last authors to enhance the international visibility of the team and to be able in the future to apply for competitive international grants. The team would also benefit from increasing the number of international researchers. The public outreach may be increased.
The quality of publications of PhD-students can be improved, avoiding to publish in putative 'predatory journals' (i.e: Cancers; Cells…).
The committee encourages the team to maintain their multidisciplinary and translational approach.

Team 6: Autophagy pathway and intracellular compartments dynamics

Name of the supervisor: Etienne Morel

THEMES OF THE TEAM

The team "Autophagy, endomembranes & cellular dynamics in stress response" has been officially created in 2019. The team 6 research is dedicated to study the integrated molecular aspects of cellular responses to stresses, with a specific focus on endomembranes mobilization and autophagy pathway.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous evaluation was performed when the team changed directorship, after the retirement of Patrice Codogno, a world authority in the role of phosphatidyl inositol in Autophagy.
A) The group should aim at keeping the same level of production and link with non-academic partners.
B) The new configuration of the team for the next contract and the change of group leader will be a challenge.
C)The new PI has to establish his leadership. The team should strive to attract a full-time researcher and to obtain an engineer/technician position.
D) The group should build on his strong expertise in cell biology.

All these recommendations have been implemented by the team.

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

Staff Total	**6**
Staff scientists	1
MCU/PU/PH	1
Technicians and engineers	1
Post-doctorants	1
Ph.D students	2

EVALUATION

Overall assessment of the team

Overall, under Etienne Morel's management, the team has excelled, addressing previous recommendations and maintaining excellent scientific productivity with twenty original publications in high-profile journals. With ANR, FRM, EU ITN support, and industry ties, the team's long-term strategy, including Dr. C. Delevoye and Dr. A. Claude-Taupin recruitment, is excellent. The Scientific project of the team is original and pertinent, although potentially too dispersive. The team needs still to be more ambitious with regards to ERC funding in order to reach an outstanding level.

Strengths and possibilities linked to the context

- National and international recognition
- High-level publications
- Broad expertise, from biochemistry of membranes to epithelial biology
- Secured funding
- Local, national and international collaborative network
- Excellent lab training
- Original projects
- Excellent microscopy and image analyses tools
- Option to combine different cell biological processes (but this is also a weak point; see below)

Weaknesses and risks linked to the context

No ambition towards ERC applications. This risks the financial stability in longer term. It is also a measure for distinction.
Risk of dispersion in the multiple pathways studied. In competitive fields, focus is critical.

Analysis of the team's trajectory

Compared to the report, the situation of the team has evolved with a senior permanent researcher leaving the team and a more junior one being recruited. This equilibrates the team and provide an excellent prospective, with interesting projects in a well-funded and staffed environment. A higher ambition level (EMBO membership, ERC...) could help in further establishing the team. Some focus on parts of the total cell biology is advised as this will help in further establishing the team as an international top player.

RECOMMENDATIONS TO THE TEAM

Attention should be paid to a stronger integration of the projects led by the different researchers, in particular the arrival of Cédric Delevoye should be carefully thought to find strong overlaps in the different projects. The integration of Aurore Claude-Taupin in the team's project should also be a priority. A clarification of her expectations and of the team leader ones should be done immediately to avoid conflictual situations in the long run. Despite what the group leader thinks, application to ERC funding should be done to give a strong architecture to its projects and reach a higher level of publications and national and international visibility.

Team 7: Pathogenesis of systemic infections

Name of the supervisor: Xavier Nassif & Alain Charbit

THEMES OF THE TEAM

This team uses state-of the-art approaches to study the microbial pathogenesis of systemic infections induced by extracellular bacteria (i.e, *Neisseria meningitidis*) and intracellular *Francisella tularensis*. Research on *N. meningitidis* has mainly focused on the molecular interactions between the bacterial pili components and host cell receptors with a strong emphasis on glycan contribution. Research on *F. tularensis* has emphasized the role of metabolic pathways in the virulence of bacteria. A third research axis has been more recently developed on *Staphylococcus aureus* and addresses the molecular mechanisms of adaptation of the bacteria in the context of chronic colonization of cystic fibrosis patients.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

There were no recommendations from the previous report.

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

Staff Total	**13**
Staff scientists	1
MCU/PU/PH	4
Technicians and engineers	3 permanents + 1
Post-docs	0
Ph.D students	4

EVALUATION

Overall assessment of the team

The team is excellent and has published a steady stream of top-quality publications involving most doctoral and post-doctoral trainees and collaborators from the best teams working in the field. The team has clearly an international recognition in microbial pathogenesis on *Neisseria, Francisella* and now on *Staphylococcus*. The team has succeeded in developing excellent basic research with both a clinical and applied vision. Financial support has been secured with several grants for the coming years.

Strengths and possibilities linked to the context

· International recognition in the field of microbial pathogenesis
· Excellent capacity to disseminate original work in top level journals
· Remarkable mentoring activity of PhD students
· Attractiveness of post-doctorants
· Excellent funding raising to support research

PhD students and postdoctorants have obtained first author publications in top-ranked journals, showing that mentoring is productive. The senior scientists also signed publications in dominant positions. This is an excellent balance of the work resources and the recognition of the leadership of projects. The team articles as principal authors are in top level journals including Nat Comm 2017, PloS Pathogen 2017, PloS Pathogen 2018, Nat Comm 2019, J Infect Dis 2019, Clin Infect Dis 2019, PNAS 2020, PNAS 2021, PloS Pathogen 2021 x2 or J Infect Dis 2022. The team has also disseminated through several reviews such Nat Rev Microbiol, Cell Microbiol or Trends Microbiol. Notably, the team contributed to clinical database for typing *Staphylococcus epidermidis*

The team has a unique expertise in INEM on host-pathogen interactions, particularly in molecular and cellular microbiology, biochemistry, genomic and metabolomic analysis. They have developed specific bacterial genetics to study the pathogenesis at the cell and host level using innovative approaches to imaging and molecular analysis. The team has also capitalized on the translation research on Staphylococcus.

The team has attracted substantial funding mainly from national sources, seven ANR projects, 1 ANRS and 2 DGA-Inserm PhD fellowships.

Weaknesses and risks linked to the context

See recommendations

Analysis of the team's trajectory

The future team Host-Pathogen Integrative Biology team will be led by two principal investigators Mathieu Coureuil and Anne Jamet and will organize onto two axis:

· Study of the role type 4 pili of *N. meningitidis* interaction with host
· Characterize the diversity of virulence traits of *S. aureus*

The first axis will explore the molecular and structural determinants of pili components that promote host cell signalling, the membrane receptor and scaffold promoting the intracellular signals, and the impact of signalling on blood vessel physiology.
The second axis will aim to develop translational research that combine *S. aureus* genomic analyses with patient data (microbiology and immunomonitoring) in order to extract unbiased hypothesis on specific virulence traits, patient stratification and co-evolution of bacteria in chronically infected patients.

Anne Jamet, an associate professor and hospital practitioner, has recently secured an interface contract with Inserm to dedicate more time to the research team.

Mathieu Coureuil is a full-time research director at Inserm and is member of the scientific committee of Inserm on Infection and Immunity, the national body that evaluate research and recruit young scientists.

For the next term, the human resources are secured and the recent ANR fundings will allow to develop an original and ambitious research program.

RECOMMENDATIONS TO THE TEAM

The Committee recommends that the future team continue its excellent research in microbial pathogenesis using a hypothesis-driven approach rather than relying solely on omics. In addition, the Committee encourages the team to broaden its research to include other pathogens and areas of basic or clinical research. The Committee also recommends that the new team leaders establish collaborations with non-academic partners. Finally, the expert committee suggests that dissemination activities to the general public be developed.

Team 8: Integrative Neurobiology

Name of the supervisor: Franck Oury

THEMES OF THE TEAM

Inter-organs communications and hormonal factors control brain functions and aging.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The overall evaluation of the team during the previous report was excellent. No major weaknesses have been identified. One of the recommendations of the previous report was to attract a permanent scientist to further foster the success of the team. Accordingly, the team recruited a junior researcher (CRCN-CRNS) in 2023.

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

Staff Total	**10**
Staff scientists	1
MCU/PU/PH	1
Technicians and engineers	2 permanents
Post-docs	3
Ph.D students	3

EVALUATION

Overall assessment of the team

This is an excellent team, which leverages an original integrative approach in neurobiology. The project uses genetics, behavioral analyses coupled to various molecular methodologies, to study different target regions of hormonal factors, like the hippocampus. The scientific output and reputation are excellent and the team is able to attract high-quality recruits. All PhD students published first-author original manuscripts. The team was able to secure an impressive amount of external fundings (5.2 M€), which reassures about the feasibility of the ambitious projects for the next term.

Strengths and possibilities linked to the context

The team, which comprises ten people with a 50% female/male ratio and a high ratio of foreign researchers, produces high quality publications and has gained more recognition through its organisation and participation in international meetings. The team has an excellent publication output, with articles published in a range of high-quality journals as leading (first/last) authors. Over the last 5 years, the Team has published 26 papers. four are papers in revision (Cell metabolism, Autophagy, Nature Aging and Cell Death and Dis.).
The large number of collaborative papers highlights the involvement of the team in collaborative networks. This together with the significant amount of invitation to present the results to more than 50 International and National Meetings highlights the great visibility of this Team.

The team has obtained numerous fundings (15 grants and 7 internationally recognized awards) between 2017 and 2022, for a total value of €5.2 M.

The team shows an excellent involvement in supervision and training activity with six PhD-students and ten supervised Masters during the last five years. PhD students complete their studies in good time and go on to scientific or allied careers. PhD students publish as first authors at least one paper (sometimes 5).
The team shows an excellent valorisation with eight filed patents. Moreover, the team is involved in the creation of a start-up with the group of L. Legai-Mallet (IMAGINE Insitute- Necker campus).

Excellent management of the Team (weekly lab meetings, journal clubs, general lab organization, tutoring sessions for M2 students to prepare them for oral presentations and report writing).

The team stands out by the quality and quantity of its non-academic interactions. Franck Oury was a consultant for Merck and Digitalis ventures, and received invited lectures at pharmaceutical companies. He is member of the Scientific Advisory Board of the SEN-OA, which is developing new senolytic treatments to treated age-related skeletal and brain disorders. He also contributes to the scientific and technological partnership (COSMIDIX) between France and Singapore engaged by the French Research Minister.

Dissemination to the general public concerns school children sensitization to research professions by team researchers, and general population sensitization to various healthcare issues, participation to several TV documentaries and to annual events such as la Fête de la science.

6 patents delivered

Weaknesses and risks linked to the context

The team is only composed by three PI's and most of the chronophagic administrative activities are performed by F. Oury.

The projects have a high translational potential, however the relationship with the Hospital is still weak. Improving an interface with the hospital should be a priority over the next period.

Analysis of the team's trajectory

The "Integrative Neurobiology" team has been created in 2015, following an international call and an evaluation by the SAB of the INEM. The overall research interest of the Team is to understand the functional impact of inter-organs communications and hormonal factors for the control of brain functions and aging.
The research projects are articulated around 3 main and well-focused questions, with a strong clinical valence. Each theme is built on solid preliminary data, rational strategies, international collaborations and highly integrative approaches.
The Scientific projection of the team for the new period of contract is to i) finalize the study in revision and in preparation, ii) pursue the investigation of the role and mode of action of Ocn and PTH/PTHrp (Short-/Mid-term) on neuronal functions, iii) open new research axes by exploring further the role of FGF23/FGFR3 system (Long-term).
The research strategy is coherent with the available resources (secured 1.5 M€ budget for the next period contract 2024-2029) of the team and with the team organization (3 permanent researchers, 2 clinicians, 2 permanent engineers and several PhD students and post-docs).
The team as an excellent network of local and external collaborations.

RECOMMENDATIONS TO THE TEAM

The team should continue to exploit their multidisciplinary research approach in collaboration with other onsite teams at INEM and IMAGINE, while keeping a focus on the primary research line that will contribute to strengthen the international visibility of the team. Along this remark, the committee would suggest to have a clear branding of the team (eg: hormonal control of ageing) that could help to recognize a specific identity of the main research field.

The team should continue to interact with IMAGINE and the neuroscience community in Paris and involve PhD-students.

Opportunities for EU funding should be pursued, as well as possible collaborations with industrial partners. This may help to obtain more post-doctoral positions that may be critically needed to reach all the goals of the project.

Team 9: Cell growth control by nutrients

Name of the supervisor: Mario Pende

THEMES OF THE TEAM

Pathophysiology of the mTOR and class III PI3K pathway in in rare diseases by studying the nutrient sensing signalling interaction

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

There was no major weakness identified in the previous reports. Strengthening the link with clinicians was a recommendation that was taken into account by the team, which now integrated a National RHU grant.

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

Staff Total	**11**
Staff scientists	3
MCU/PU/PH	1 PUPH
Technicians and engineers	2 permanents
Post-docs	1
Ph.D students	4

EVALUATION

Overall assessment of the team

This outstanding team focuses on understanding mammalian Mtor and class III PI3K pathways, exploring nutrient response regulation. The team employs cutting-edge techniques and preclinical models, earning a remarkable reputation with 3 ERC grants in the last decade. All PhD students authored first-author papers. The team's scientific influence, European integration, and exceptional training environment make it appealing. Strong industrial collaborations and participation in a RHU grant for overgrowth syndromes enhance its clinical potential and reinforce its impressive research contribution.

Strengths and possibilities linked to the context

The team has made several important discoveries on the role of Mtor/S6K1 signaling pathway in diverse biological processes, including cellular senescence, Tuberous Sclerosis Complex (TSC) disease, various metabolic diseases, such as fatty liver disease, Lipin1 deficiency, lysosomal storage diseases, Ribosomopathies and aging-related neurological disorders.
The team produces high quality publications and has gained more recognition through its organisation and participation in international meetings. The team has an outstanding publication output, with articles published in a range of high-quality journals as leading (first/last) authors.
Over the last five years, the team has published 18 papers in renowned top journals. Seven of these studies were published as corresponding authors in prestigious Journals (Nature Communications, EMBO Journal, JCI, Nature Aging). The team has a large national and international collaborative network, a great visibility and a remarkable fundraising capacity at the European level as witnessed by 3 ERC grants awarded to members of the team during the last 10 years. G. Panasyuk, a former postdoc of the lab and an ERC-Consolidator laureate, is now an autonomous group leader in the INEM Institute, spinning off the studies on class III PI3K signalling.
The team shows an excellent involvement in supervision and training activity. The great majority of PhD-students published first author papers in top-ranked journals with an average impact factor of publications from PhD students in the lab of 13, which is remarkable. Two students obtained a tenure research position at Inserm while the majority are still doing Postdoctoral trainings, with the exception of T. Rashid who is Medical Advisor-Project manager at Astra-Zeneca.

The team has created and operates a metabolomics facility with LC-Ms and Seahorse instruments.
In terms of Institutional tasks, Mario Pende is a Co-Director of the Cell Biology Dept. at INEM and Member of the Conseil Scientifique of the Université de Paris.
The actors and interlocutors for economic and social interactions are well defined and collaborations are in place. The team leader is actively involved in the organization of international meetings.

Weaknesses and risks linked to the context

The management of the Team has not been detailed.
The recruitment strategy of new tenured researchers is not clearly stated.
In the recent period the lab is mainly relying on short-term awards of three years (ANR, AFM).
In addition, the lab is experiencing a relative drop in the number of postdoctoral applications to join the lab.
It seems that the team's Intellectual Property (IP) is not efficiently protected, although the team's data support important drug development activities.

Analysis of the team's trajectory

The area of investigation of the team spans the research interests from cell size control, to metabolic adaptations, the pathophysiology of Mtor and PI3K signal transduction and the therapeutic implications for rare diseases.
The team leader has earned a good name recognition and has been highly productive in conducting high quality research which resulted in many interesting discoveries. Since Mtorc1/S6K1 signalling is recognized as a pathway with enormous impacts on the pathogenesis of various diseases, the team's decision to broaden its focus is logical.
In the next five years, the main mission of the team will be to coordinate its work on the fundamental mechanisms of growth and metabolic adaptations with multiple partners to exploit all the biomedical implications. The scientific program appears strong and robust and can generate original data with competitiveness at an international level. Future studies on molecular targets of the Mtorc1/S6 kinase cassette and the studies on the metabolic control of senescence sound very solid. The study of the Hippo pathway components' role in cell proliferation seems to be a new direction of the team, which is highly competitive. Nevertheless, the described objectives address novel questions, suggesting that this activity could result in important new discoveries. The studies on TSC in brain function and ependymal cell differentiation are interesting ones and certainly worth to pursue.
Each of the seven specific themes is built on solid preliminary data and/or published articles, international collaborations and highly integrative approaches including proteomic, pharmacology, biophysical and genetic approaches.
The Scientific projection of the team for the new period of contract is to pursue its research program on rare genetic diseases of the Mtor signal transduction by focussing on: i) brain pathologies linked to Tuberous Sclerosis Complex, ii) Cloves and additional overgrowth syndromes. Medical implementation of clinical trials are foreseen in collaboration with a robust network of clinical collaborations.
The research strategy is coherent with the team organization. For the next mandate, the team will be composed by three tenured researchers, 2 engineers and a significant number of non-permanent staff (4-6 PhD students, 1-3 postdocs). However, the current funding of the team does not seem to be sufficient to carry on all of the 7 axes proposed by the team.

RECOMMENDATIONS TO THE TEAM

The team should secure long term fundings and attract international postdoctoral fellows.
Further public outreach and contact with patient organizations are recommended.
Maintaining and reinforcing the interactions with the industrial and clinical world should be a priority over the next period.
Considering the work-force of the team and the currently available funds, the number of projects of the team seems a bit excessive. It would be advisable to re-focus the activity of the team on the most promising axes and set the tasks and responsibilities of researchers in a very clear way.

Team 10 : Epigenetics and development

Name of the supervisor: Marco Pontoglio

THEMES OF THE TEAM

The research of the team focuses predominantly on the transcription factors Hepatocyte Nuclear Factor 1 alpha and beta (HNF1A and HNF1B), which are proteins with a homeostatic function present in the epithelium of different organs. The team studies the mechanisms associated with HNF1 deficiency in kidney diseases, both congenital and in adults, caused by mutations in HNF1A and HNF1B genes. Through cellular and molecular approaches, the team investigates the role of HNF1B in gene regulation during kidney development and dysfunction with the goal to determine the causes of renal diseases driven by HNF1B mutations and develop novel pharmacological therapies.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

No issues to address here.

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

Staff Total	**15**
Staff scientists	2
MCU/PU/PH	1
Technicians and engineers	2 permanents + 4
Post-docs	4
Ph.D students	2

EVALUATION

Overall assessment of the team

The team has an excellent scientific output and reputation. This is reflected by high-quality recruitment and frequent invitations to conferences. The team's organization is excellent and involves training of clinical and fundamental researchers, facilitating the interaction within the hospital and the translational potential of its research. The team has established several partnerships with pharma companies. In terms of scientific strategy, the projects are excellent and well defined, but incorporating models closer to the human disease should increase their translational impact.

Strengths and possibilities linked to the context

Dr. Pontoglio leads this well-established research group that is a leader in their field, with the focus on the biology of hepatocyte nuclear factor (HNF) transcription factors, especially relating to kidney development and disease. Over the last decades, Dr. Pontoglio has published numerous key original papers on this topic. The Team also stands out for its internationally recognized contributions to scientific meetings. The Team applies multidisciplinary approaches to define the function of transcription factors associated with renal diseases. They have recently developed a novel screening method coupled with HNF1B biosensors to determine the genes that regulate HNF1B activity.

Weaknesses and risks linked to the context

One potential weakness is that the great weight of the Team's research relies on expiremental models. So it is good to hear that the team are beginning to translate insights into human disease, as examples using organoid technology and genomics in affected people. A related weakness, however, lies in the limited human resources available.. Moreover, the identification of Team leader successors is not clear.

Analysis of the team's trajectory

Dr. Pontoglio leads a solid science team with postdoctoral scientists and postgraduate students. The scientific trajectory of the Team is clear, solid and focused as it has established effective strategies to pursue research objectives in experimental and translational science. The scientific production in terms of last author papers has somewhat decreased in the few years but there is one such manuscript under revision that is expected to be published in 2024.

RECOMMENDATIONS TO THE TEAM

To continue the high quality of research. More translation of the excellent experimental orientated laboratory results into human diseases is recommended. The recruitment of new scientific staff to enhance the Team's competitiveness and to reinforce its future identity is warranted. The Team currently has one scientific lead but should consider evolving to having two research co-heads, namely one clinician and one basic researcher. The incorporation of a clinician with science research experience would give the best chance to maximize the translational potential of the Team's excellent research. Although funding has been secured for the next years, the addition of academic grants (European or French) would contribute to maintain the excellent trajectory of the Team.

Team 11: Cystic Fibrosis and other epithelial respiratory protein misfolding diseases

Name of the supervisor: Isabelle Sermet Gaudelus

THEMES OF THE TEAM

The team works mainly on two chronic pulmonary diseases, Cystic Fibrosis (CF) and Alpha1Anti-Trypsin Deficiency (AATD). Worldwide estimations of the prevalence of CF are respectively of 200,000 patients with CF and of 3.4 million patients with symptomatic AATD.
The team has adopted an integrated approach to identify protein-protein interactions (PPIs) of misfolded proteins, taking F508del-CFTR and Z-A1AT as models. They aim to disclose novel therapeutic targets, potentially shared between misfolded proteins, identify compounds able to remodel these interactions and restore normal protein biogenesis, in order to implement personalized therapeutic strategies.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

No specific recommendation can be found in the previous recommendations section. The scientific production has been judged as outstanding.

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

Staff Total	14
Staff scientists	1
MCU/PU/PH	4
Technicians and engineers	2 permanents + 2
Post-docs	4
Ph.D students	1

EVALUATION

Overall assessment of the team

The team production is excellent. The team studies misfolded protein-protein interactions and aims at developing therapeutic approaches that correct their folding. The group combines basic and clinical research, providing new insights on ERAD-mediated restoration of misfolded Z-AAT secretion and trafficking of F508del-CFTR mutant. The team has identified several potential biomarkers that could be used for personalized therapies. The team was highly productive through participation in large collaborative clinical research projects collaborations with major centres and societies.

Strengths and possibilities linked to the context

The team published 140 papers in the past five years, a high output, though a low percentage in high-impact journals. They've made important discoveries, including novel CFTR potentiators/modulators and new interaction partners. Some findings on using CFTR activity as biomarkers are validated in a small number of patients, showing the project's impact. With a good mentoring record and excellent funding from diverse sources, the team developed long-term collaborations with major international centers and has a strong interaction with Necker Hospital's clinical department. They hold two patents protecting methodological approaches.

Attractiveness
Senior members' international recognition enhances the team's appeal, with key roles in the European Society for CF and Clinical Trial Network. Ongoing collaborations with over ten centers globally and successful outcomes from Canadian researchers' sabbatical contribute to attractiveness.

Among four Post-Doctoral researchers, one joined a pharmaceutical company, and three are expected to join permanently either team 11 or a pharmacology team at Hospital Foch. The team successfully trained four PhD students during this evaluation, all gaining permanent researcher positions. They also trained twelve Masters. Two technicians received training; one gained a permanent position in another unit, and the other is involved in a PhD at a Quebec university.

Production: The team's integrated approach targets pathways, biomarkers, and therapies for CF and AATD. They demonstrated that modulating ERAD interaction with the cytoskeleton restores biogenesis of misfolded F508del-CFTR and Z-AAT. Basic research focuses on understanding F508del-CFTR and Z-AAT's protein-protein interactions with ERAD complexes to identify potential shared pharmacological targets. At the translational level, personalized therapy implementation for CF patients and understanding the success of amino acid opotherapies in rare pediatric ARSsopathy diseases are priorities. The team launched a compassionate program for severely symptomatic pwCF with potentially responsive but currently non-eligible genotypes based on CFTR activity recovery in patients' nasal epithelial cells.

Inclusion in Society
The team leader coordinates standardizing Clinical Research Procedures within the Clinical Trial Network, with a major aim to develop a patient-directed outcome measure for clinical trials and practice. They launched 2 patents regarding methionine substitution and peptide therapy in CF. Team members are involved in ethical committees for human, animal, or organoids. They wrote guidelines for antenatal diagnosis, considering pregnancy interruption, and participate at the European level in fighting access inequity. Team members engage with patient associations and disseminate science in medical general media.

Weaknesses and risks linked to the context

- The large network of collaborators and the alignments of the team's activities with them possess an extra administrative burden. This may have negative effect on the time spent for research. In the presentation there is no clear solution for this problem is indicated.

Analysis of the team's trajectory

The team has been engaged in the research area of the epithelial channelopathies and has made very important contributions both at the level of understanding the mechanism of pathogenesis and developing biomarkers and treatment protocols. The team's work has raised novel concepts about the molecular mechanisms of protein misfolding and provided novel directions to develop diagnostic and therapeutic strategies for loss-of-function protein misfolding diseases.
The future plans contain logical extensions of the previous work. It will expand the efforts of protein interactome studies to further expand the number of modulators. The team will continue its involvement in a "real world" study that collects data of patient responses on CF and CFTR modulators.

RECOMMENDATIONS TO THE TEAM

Overall the Team is performing important translational research with high success rate in the fields of protein misfolding disease pathogenesis. The field is highly competitive. In order to maintain competitiveness, it is recommended to place somewhat more emphasis on basic, "blue-sky" research activities, which have produced results that were important starting points for subsequent translational studies, where the team is especially strong.

Team 12 : Mechanisms and therapeutic strategies of chronic kidney disease

Name of the supervisor: Fabiola Terzi

THEMES OF THE TEAM

The team is involved in understanding the pathogenetic mechanisms of chronic kidney disease (CKD) with the aim of identifying new therapeutic options. In the context of CKD, the group is focused on both diabetic and non diabetic nephropathy with particular interest in autosomal dominant polycystic kidney disease (ADPKD) and Alport syndrome. The team is also pledged on the validation of new biomarkers able to predict transplant rejection and monitoring renal disease progression.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team has successfully accomplished the previous recommendations. Among those, a consistent group of 17 PhD students, has been mentored in the last six years.

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

Staff Total Staff	**25**
Staff scientists	2
MCU/PU/PH	8
Technicians and engineers	4 permanents + 3
Post-docs	4
Ph.D students	4

EVALUATION

Overall assessment of the team

The team led by Fabiola Terzi is a heterogenous group comprising basic researchers and clinicians. Their primary focus is on understanding the pathogenesis of CKD. Their research spans basic investigations and clinical approaches. The research quality of the team is excellent, boosting an impressive scientific output and 10 approved patents. The group led by Dr. Terzi is recognized as a centre of excellence in the field of CKD. Its considerable expertise in modelling CKD constitutes a significant asset; although their results must be critically assessed regarding translatability to the clinic.

Strengths and possibilities linked to the context

The research team excels not only in working with experimental models of chronic kidney disease (CKD) but also in cooperation between scientists and clinicians. The Team produces excellent scientific research publications unravelling new aspects of CKD and their research has contributed to ten approved patents. The research group continue to produce many biologically fascinating papers in high impact factor journals on the mechanisms of chronic kidney disease. In this respect, the research group is a leader in their field. Moreover, some insights are emerging relating to human CKD, for example in biomarkers. Dr Terzi is an excellent team leader and establishes good interactive relationships with team members.

Weaknesses and risks linked to the context

Usually, the Team's experiments rely on experimental models. These results, however, must be strengthened and critically assessed regarding translatability to the clinic, especially to pioneer new treatments to slow progression of CKD in people. In addition, the dissemination by team could be improved.

Analysis of the team's trajectory

Dr Terzi leads a large research Team with numerous postdoctoral scientists, technical staff. And postgraduate students. The Team is supported by numerous grants of moderate size. The planned studies of the Team align with previous research and expertise acquired in the laboratory, demonstrating consistency and feasibility. The team will employ innovative techniques to accomplish and finalize previous studies and initiating new exploratory research.

RECOMMENDATIONS TO THE TEAM

The standard of research work should continue at the current high level. The team achieved excellent results understanding the development and progression of CKD, mostly in experimental models. The research activity, however, could be more focused on translation to clinical settings. The combination of the knowledge acquired by the team with a more translational approach could lead to ground-breaking research in the field of CKD. Furthermore, the research team could boost dissemination by engaging in scientific meetings, seminars, and workshops, and establishing new collaborations beyond pharmaceutical companies. The Team leader in the next decade should focus on strengthening the mentoring of emerging leaders to ensure a seamless and effective transition of future Team leadership.

Team 13 : Innate and adaptative immune pathways in autoimmunity and autoinflammation

Name of the supervisor: Peter Van Endert

THEMES OF THE TEAM

The team of Peter van Endert is an expert on mechanisms leading to autoimmune pathogenesis of Type 1 Diabetes and antigen presentation by MHC class I molecules. He has a long history of basic research lines focused on abnormal antigen processing and presentation responsible for autoimmune T cell activation in T1D. In 2016 Dr Julien Diana joined the team bringing a large expertise in the field of innate immune regulation and, specifically, the role of the intestinal environment and commensal microbiota in the pathogenesis of T1D. An additional PI who recently joined the team, Dr de Lonlay, brought expertise in on a new line of research (inflammation in rhabdomyolysis) and also a significant clinical expertise that can be critical in translation of laboratory results.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team has followed most of the previous recommendations.

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

Staff Total	**19**
Staff scientists	2
MCU/PU/PH	2
Technicians and engineers	2 permanents + 5
Post-docs	3
Ph.D students	5

EVALUATION

Overall assessment of the team

The team has made important contributions to the field, in particular highlighting some possible mechanisms involved in the pathogenesis of T1D based on own fundamental work. The PI (PvE) and co-PI (JD and PdL) have excellent track record of publications, with work published in high-impact journals and they are renowned experts in their different fields of research. Capacity to secure funding and to contribute to the high visibility of the host institution is very well demonstrated. The integration between the three main lines of research is limited and could be further exploited.

Strengths and possibilities linked to the context

The team of PvE has conducted important basic research projects on the role of abnormal antigen processing and, specifically, the role of trimming aminopeptidases, crosspriming metallophilic macrophages and mitochondrial antigen presentation in the pathogenesis of T1D. On the other hand, Dr Diana worked on the crosstalk between gut microbiota and the role of anti-microbial peptides produced by intestinal cells and beta cells for modulation of T1D. The field of intestinal modulation of T1D is very timely and Dr Diana's research recently expanded on the role of the intestinal environment in T1D modulation with preclinical work on the role of probiotics that could have high translational potential. Dr de Lonlay also contributes important and original lines of research in rhabdomyolysis with high translational potential.

Weaknesses and risks linked to the context

The team focuses its effort on different lines of research related to T1D and inflammatory diseases, however their effective integration in terms of common scientific questions, shared methodologies and experimental models is not fully demonstrated. In competitive fields of research, the research teams are too small unless a mode of collaboration or integration of research lines is established.

Analysis of the team's trajectory

The three PIs of the team and their lines of research have been very productive in terms of scientific output in significant peer reviewed scientific journals. The research has important translational potential. Some doubts concern the future perspectives of the team. The main PI will retire in a few years and in the meanwhile will join the team of Siman Fillatreau. However, the future research activities of the two co-PI and the possibility for them to lead a significant research team and to receive appropriate institutional support is not clearly demonstrated.

RECOMMENDATIONS TO THE TEAM

The lines of research developed by the team are very original and relevant and fully integrated with the institutional research activity. It will be important that the team will continue to perform the high-quality research beyond the endpoint of Dr van Endert's retirement and develop already a program with more integrated research to be evaluated in order to remain a scientific top activity. An evaluation of this program by the Institute or an external body may help in ensuring a significant scientific activity by the team. This may include finding a replacement for Dr van Endert or investment in other activities relevant within the Theme.

Team 14 : Host-microbiota interaction

Name of the supervisor: Pamela Schnupf

THEMES OF THE TEAM

Team 14 " Host-Microbiota Interaction" is led by Dr Pamela Schnupf. Its focus is on a family of filamentous intestinal bacteria known as Segmented Filament Bacteria (SFB). Although the role of these bacteria in the Th17 response and IgA production has been known for some time, only recently has it become possible to study them due to their previous uncultivability. The team working on this is relatively new, having started in 2020. The team aims to study the SFB cycle and its molecular and genomic features, as well as to characterize the relationship between SFB clades and host specificity. Additionally, the team aims to decipher the cross-talk with immune components.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team was not in place at the time of the previous report and was established in January 2020.

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

Staff Total	**6**
Staff scientists	1
MCU/PU/PH	0
Technicians and engineers	1 permanent + 1
Post-docs	1
Ph.D students	2

EVALUATION

Overall assessment of the team

Team 14 demonstrated a high level of skill in its research on SFB, a challenging topic due to the difficulty in growing the bacteria and the lack of genetic tools for mechanistic approaches. The project is ambitious and aligned with the goal of advancing basic research in high-risk projects. The team do not publish a lot, but in highly regarded journals. Dr. Schnupf has received outstanding funding from the ERC and the Bill and Melinda Gates Foundation. Dr. Schnupf has been awarded several prizes, including the Foundation Bettencourt. The team has an excellent trajectory.

Strengths and possibilities linked to the context

· Unique expertise in cultivating SFB
· Impressive expertise in axenic and gnotobiotic mouse models
· Remarkable capacity to raise funding

The team has made an original contribution to the biology of SFB and published an article (Nat Microbiol 2020) describing the life cycle of SFB and the production of the flagellated form of bacteria that may modulate the immune system. During the 2020-2023 term, the team focused on three main areas of research. Firstly, they conducted an investigation into the relationship between flagellum/motility and immune stimulation. Secondly, they identified the molecular determinants of SFB (tip) and the host receptor that contributes to the attachment of bacteria to intestinal epithelial cells. Finally, they mapped the global diversity of human SFB using genomic approaches. These achievements are expected to result in publications in top-level journals. Additionally, the team published reviews in Curr Opin Immunol and Curr Opin Microbiol. In 2019, Dr Schnupf obtained her HDR and has since directed three PhD students. One of them has already defended their thesis, and another is expected to defend soon.

Weaknesses and risks linked to the context

· Absence so far of genetic tools in SFB for mechanistic approaches.
· Limited interactions with INEM teams and external collaborations
· Difficulties to hire post-docs
· Some unbalance between staff number and project axis

Analysis of the team's trajectory

The team objectives for the next term are to continue developing research on SFB though 5 axis:
· Explore the role of SFB flagellum in motility and immunoregulatory activity
· Investigate the ultrastructure of SFB throughout the bacterium cycle
· Identify the SFB adhesin promoting interaction with gut epithelium and surface proteins (such S layer)
· Develop unique tools to modify genetically SFB (for basic research and vaccine development purposes)
· Characterize the human SFB

Each axis research is conducted by a PhD or Post-doc.

RECOMMENDATIONS TO THE TEAM

As the team has substantial financial resources, it should consider hiring more postdoctorants and/or engineers. Another option, given the critical size of the team, would be to refocus research projects, taking advantage of the environment of the research unit at Necker. As specialists in microbiology and biochemistry, collaboration with the INEM team to analyze the immunostimulatory activity of the SFB would be a valuable opportunity.

Team 15 : Translational and Personalized Medicine Laboratory

Name of the supervisor: Guillaume Canaud

THEMES OF THE TEAM

The research interest of the Team focuses on the genetic and therapeutic aspects of overgrowth syndromes. The main goal is to elucidate the pathophysiology of rare disorders involving the PIK3CA/AKT/mTOR pathway to discover biomarkers and potentially new therapeutic targets in order to offer personalized medicine to patients suffering from overgrowth syndrome and vascular anomalies.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

This is a newly established research Team at INEM. Its leader Dr. Canaud transitioned from Terzi's Team and gained independence in 2019 after securing an ERC starting grant.

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

Staff Total	**17**
Staff scientists	
MCU/PU/PH	1
Technicians and engineers	5 permanents + 4
Post-docs	2
Ph.D students	5

EVALUATION

Overall assessment of the team

The team, led by a brilliant leader with great visibility, performs research on PIK3CA-related overgrowth syndromes. Publications in prestigious journals and numerous awards and grants testify the team's excellence to understand these disorders. The team performs outstanding translational research with relevant clinical impact. Dr. Canaud coordinates the RHU COSY, a consortium project aimed at transforming the outcome and medical care of patients with overgrowth syndrome. The team is highly qualified to execute its research proposal with maximal efficacy. The team's quality is outstanding.

Strengths and possibilities linked to the context

The team is at the forefront of research in overgrowth syndromes and vascular anomalies, with worldwide recognized visibility. The Team's scientific activity is an excellent example of translational research thanks also to a strong connection with the clinic. The team has published several articles on international peer-reviewed scientific journals with a high impact factor, including Nature, Science Translational Medicine, Science Advances, thus confirming the high standard and quality of research. The team has remarkable financial resources (>20M €) mainly obtained through calls for international projects (ERC) and from national agencies, including ANR. Dr. Canaud has been awarded three ERC grants and his Team has received numerous national and international prizes and awards. The team has a close collaboration with pharmaceutical companies and biotechs and also boasts a high ratio (>60%) of licensed to submitted patents. This is useful for studying drug repositioning and for transferring experimental results to the clinic. The dissemination of the results to the general public is solid.

Weaknesses and risks linked to the context

There are no major weaknesses. One possible concern, however, is the proposition to use several experimental models rather than judiciously blending this approach with, for example, developing human organoid models. The latter may provide human-specific insights.

Analysis of the team's trajectory

Dr. Canaud leads the evolving group that includes both scientists and clinical researchers. He spends around half his time on clinical duties. The team has attracted trainees coming from around the world. The scientific program of the team for the future is innovative with a high potential for transfer to the health care of patients with genetic overgrowth syndromes and vascular malformations. The research proposal is very focused and well supported by solid preliminary data. The extension of the focus to other overgrowth syndromes, besides PROS, associated with RAS and AKT mutations, for which no specific treatments have been currently approved, further strengthens the relevance of this translational research in the field of these rare disorders. The research plan is generally well conceived, and the experimental approach is based on consolidated technologies.

RECOMMENDATIONS TO THE TEAM

To continue the high level of research. To consider using human organoid. To consider partnering with a senior scientist who could supervise and direct some of the laboratory work, especially given that Dr. Canaud has significant time-consuming clinical duties.

Team 16 : Immune response and danger signals

Name of the supervisor: Benedicte Manoury

THEMES OF THE TEAM

The team focuses on four main objectives: 1) to identify new partners of interaction for UNC93B1 and to investigate the molecular mechanisms by which UNC93B1 shapes their function, 2) to characterize new sub-cellular compartments where endosomal TLRs traffic, 3) to evaluate the actions of TLR9 in microglia versus peripheral immune cells during development of Alzheimer disease(AD) using specific models of experimental and in human AD pathology and 4) to investigate the role of TLR9 in immune tolerance and response to cancer.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team was not constituted at the time of the previous report and was integrated within Peter Van Endert team. It emerged in January 2020.

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

Staff Total	**6**
Staff scientists	1
MCU/PU/PH	0
Technicians and engineers	1
Post-docs	2
Ph.D students	2

EVALUATION

Overall assessment of the team

B. Manoury is an internationally known researcher in antigen presentation and TLR signaling. The team has made seminal contributions published in high-profile publications during the last mandate. The projects are originals with relevance to health and diseases, although they are mostly performed in mouse models. The team is small and most of its recent work was done in collaboration with other teams, including 1 from INEM. The team has sufficient funding to carry on its activities until 2027. Overall, the team activity is very good given its size, however it still needs to gain momentum.

Strengths and possibilities linked to the context

- National and international recognition
- Strong national collaboratives network
- Training of students and mentoring of post-doctorants
- Multidisciplinary
- Projects originality

Weaknesses and risks linked to the context

- Small team
- International competitivity of the field
- No obvious clinical translation
- Limited interactions with other INEM teams
- Development of many projects according to the size of the team

Analysis of the team's trajectory

The team led by B. Manoury is a relatively new and independent team, but it has struggled to gain significant size during the evaluated period. Over this time, the team has published seven main publications, primarily in collaborative efforts (EMBO Mol Med 2022, J Cell Sci 2020). Notably, the most substantial contributions were made in 2017 (3 publications Nat Immunol, Nat Comm, Nat Comm) and 2018 (1 publication in Nat Comm), raising concerns about the team's productivity as it approaches the next mandate, although the COVID19 crisis might have contributed to decrease the overall activity of the team. It is important to highlight that the team has a collaborative article in revision in J Exp Med and a manuscript submitted to eLife as main contributor. Overall, the team activity is very good given its size, and it needs to strengthen its research by increasing its size and may be refocussing on key projects.

Significant changes are on the horizon for the team post-2024. The addition of two seniors staff scientists (DR2 Inserm and MCU Univ Paris Cité) and associated students will substantially increase the team size to 11 members. This growth will coincide with a relocation to new lab space, complemented by the anticipated, but not guaranteed, appointment of a permanent laboratory technician. These developments are expected to infuse the team with much-needed energy and resources. Importantly, B. Manoury and the 2 new Pis have secured substantial funding to start their activities in the upcoming term, including 2 ANR grants and 2 INCA-PLBio grants. This funding serves as a significant assurance of success in conducting cutting-edge research.

While the arrival of the two senior scientists brings their own research themes and funding, it also raises concerns. Despite a shared interest in phagocytic mononuclear cells, it is acknowledged that this convergence might dilute the current identity of the team leader and diminish the prominence of her personal projects within the expanded team. Balancing these dynamics will be crucial for maintaining cohesion and ensuring a harmonious integration of new elements into the team's research landscape.

RECOMMENDATIONS TO THE TEAM

The team should improve its productivity by maybe reducing the number of projects carried out and increasing its size. The new organization of the team from 2025 on, looks like the creation of three groups under the same umbrella and great care should be given to integrate the projects and defines before end the expectations of the senior scientists to avoid dispersion and maintain the integrity and the quality of the research developed by B. Manoury in the future. A particular effort in increasing the publications level to be able to apply to ERC funding has to be undertaken. Hiring a technical staff will be essential to reinforce the internal team collaboration and the day-to-day activity of the laboratory.

Team 17 : Mechanisms of Nutrient Sensing

Name of the supervisor: Ganna Panasyuk

THEMES OF THE TEAM

Class 3 PI3K signalling in metabolic control.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

New team. Not applicable.

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

Staff Total	11
Staff scientists	1
MCU/PU/PH	2
Technicians and engineers	3
Post-docs	3
Ph.D students	2

EVALUATION

Overall assessment of the team

The team, established a few years ago with an ERC Consolidator grant, is led by a highly successful researcher who transitioned from Dr. Pende's lab (Team 9) to independence. Despite sharing the class III PI3K focus with Team 9, the team maintains independence. In the past 4-5 years, they made spectacular scientific strides, particularly discovering the nuclear role of class-III PI3K. This groundbreaking study revealed the kinase's fundamental role in circadian gene expression control, challenging its known functions in endocytosis and lysosomal autophagy. The group also advanced projects on biliary atresia and molecular studies on class-III PI3K's role in lysosomal storage disorders. Consolidating its position in the PI3K signal transduction field, the team demonstrates excellent research capabilities and shows potential to become a leader in the scientific area.

Strengths and possibilities linked to the context

- Past and ongoing research activities address important and challenging scientific questions and resulted in findings that established novel concept.
- The team is led by a highly promising PI, who pursues original and interesting ideas.
- The results of the research have high scientific impact and possibly clinical impact.
- The group has published in top-quality journals.
- The PI has been awarded a highly competitive ERC Consolidator grant.
- The team has already established very strong international collaborations.
- The team has an international character with students and post-docs from many different countries.
- The team work has also resulted in one patent and secured a contract with industrial partner for pursuing the project on biliary atresia pathogenesis.

Weaknesses and risks linked to the context

- The team could not succeed to obtain permanent research staff, that would support continuity.
- Some of the team members work part time in the hospital, which may be beneficial for pursuing translational aspects of some research projects but not optimal for basic academic research.

Analysis of the team's trajectory

As described above the team has been recently established by a PI who was post-doctoral fellow in team 9 of the unit. The team pursues a new research angle in PI3K biology and has already produced ground-breaking new discovery. Considering the success of the team so far, it is seen very positively to assist some of the very talented young researchers to gain full independence within the unit, as it is the case here. The scientific quality of the research is high, which provides promise for successful future expansion of the team and a good chance that the PI will develop into a leader of the PI3K field.
The questions addressed in the ongoing efforts include the understanding of the functional significance of the different intracellular pools of class-III PI3K in physiological and pathological conditions and studies on temporal dynamics of class-III PI3K in metabolic rhythmicity and energy utilization. A third ongoing activity involves studies on PI3K signalling in biliary diseases and specifically in obstructive biliary atresia. All of these activities are considered high-risk / high-gain frontier research efforts.

RECOMMENDATIONS TO THE TEAM

The team is to be praised for its achievements so far and has a good outlook for further development. It is recommended to keep the international character of the composition and further strengthen its established international collaborations.

Team 18 : Laboratory of System Biology

Name of the supervisor: Sagi Shapira

THEMES OF THE TEAM

The new team plans to explore the interplay between the immune system and the mucosal epithelia in response to viral infections by using both experimental biology and computational approaches. Two axis of integrative research are conducted:
· Deciphering the viral strategies for hijacking cellular machinery
· Decoding innate immune cell trajectories during viral infection

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

It is not applicable since the team was created in January 2022.

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

Staff Total	**5**
Staff scientists	2
MCU/PU/PH	1
Technicians and engineers	1 permanent
Post-docs	1
Ph.D students	0

EVALUATION

Overall assessment of the team

Dr. Shapira, an exceptional PI, focuses on experimental and computational approaches to study genetic and molecular interactions among epithelia, immune cells, and viruses. Achieving international prominence, he joined INEM in 2022, where he is currently rebuilding his team. Initial difficulties, exacerbated by COVID-19 and slow integration into the French environment, have impacted its productivity. Issues in recruiting fellows or retaining permanent staff pose risks, that need to be mitigated by integrating better into INEM, enhance interactions, and expanding its size for sustained momentum.

Strengths and possibilities linked to the context

- International career and visibility
- Articles of outstanding visibility (Immunity 2017, Nat Immunol 2017, Cell 2019, Nat Med 2020, Cell Systems 2020)
- Established leadership in Systems Immunology
- Integration in Graduate programs in US
- Start-up package with 3 permanent staffs
- Coordination of computational Hub in Paris

Weaknesses and risks linked to the context

- Difficulties in team building in the French system
- PhD and post-doc recruitment

Analysis of the team's trajectory

The research project will follow 4 axis:

- Identification of elements that regulate transcriptional responses to infection and control pathogen-host relationships
- Analysis of pathogen evolution at a systems level
- Uncovering genetic and functional determinants of human infectious disease
- Development of new tools for manipulating synthetic cell circuits

The team needs to specifically focus on specific pathogen, disease and system to be competitive.
At the beginning of the next term, the team will be composed of the principal investigator, one senior scientist and one technician. To build further, particularly on the four axis, recruitment of PhD students, post-docs and technical staff dedicated to experimental and computational approaches is essential.
Notably, the team has two manuscripts in revision in Immunity and Cell that will contribute the team trajectory.
The team has secured a charity fund (FRM) until 2026 and is involved two consortia: Necker Consortium for Quantitative Biology and Fédération de Recherche to build a Hub. The leadership in the development of a computational Hub should contribute to build the team

RECOMMENDATIONS TO THE TEAM

The team has to capitalize on recruitment of specific staff and students to be operational and competitive.
The raising of funds needs to be improved to perform cutting-edger research and attract talents. Application to ERC grants is expected.
The collaborations with other teams of INEM is essential since they will contribute to cross-fertilization with regards to experimental and computational research. Similarly, collaborations with the Center IMAGINE will have the same impact on some axis of the project. The project can serve to implement the clinical-, economical and societal-oriented activities of the team.

Team 19 : Leukomotion Lab

Name of the supervisor: Pablo Vargas

THEMES OF THE TEAM

The Leukomotion lab aims at dissecting the cellular mechanisms that control leukocyte and especially neutrophil trafficking in the organism, with the ultimate goal of translating this knowledge into innovative therapies. The team uses microfluidic technologies in combination with light microscopy to identify cellular mechanisms altered in human pathologies and to develop new technologies tools for diagnosis and drug discovery through phenotypic screening.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The group has been created at the Institut Curie in 2015 with the support of an ANR JCJC, followed by a scientific co-direction of the System Biology of Cell Polarity and Cell Division group with Matthieu Piel (DR1, CNRS). Pablo Vargas and his team just recently moved to INEM (2022) after responding to an international recruitment call and therefore were not included in the previous HCERES evaluation report.

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

Staff Total	**5**
Staff scientists	1
MCU/PU/PH	
Technicians and engineers	1 permanent
Post-docs	1
Ph.D students	2

EVALUATION

Overall assessment of the team

P. Vergas, a respected cell motility researcher expert in microfluidics, leads a small but well-funded team at INEM. While interactions with its previous Curie lab are unclear, its recent scientific output prior arriving at INEM is very good with mostly collaborative papers. P. Vargas focuses on identifying physiological regulators of leukocyte migration to manipulate immune responses for therapeutic use in inflammation or cancer. Its recent arrival makes a comprehensive evaluation challenging, but with Vargas's track record, positive developments for INEM and the team are anticipated.

Strengths and possibilities linked to the context

- Funding
- Unique expertise in microfluidics and cell migration
- possibility of clinical translation at INEM
- Very collaborative
- Highly original observation related to ATM and migration (but also issue; see below).

Weaknesses and risks linked to the context

- Small lab
- No permanent researcher
- little original work from the team signed as a last author
- International visibility
- limited expertise as required for determining the molecular mechanism coupling ATM to migration.

Analysis of the team's trajectory

The team needs to grow and focus on few specific projects, that can only be performed with the team's know how. The choice of ATM has a target can be a good bet, but will require technologies beyond those in the team to find the underlying molecular mechanism. This may result in further expansion of the technologies run in the team. It is in fact a 'High Risk-High Gain' project, which are the type of applications preferred by ERC. The risk of multiplying targets is to become a collaborative technology hub rather than an independent research entity. The recent arrival of the team makes its full evaluation difficult and given the funding situation and track record of Pablo Vergas, one can hope that the group will bloom during the next mandate. The group activity is very good and its leader is quite aware of these issues raised by the committee.

RECOMMENDATIONS TO THE TEAM

- Try to publish key papers and gain further international visibility.
- Focus on few projects with high potential.
- Keep an equilibrium between collaborations and personal projects to avoid to become a collaborator rather than an initiator.
- Define a strategy on how to connect ATM with migration and establish the corresponding technologies in the lab.
- Try to obtain European funding after defining a 'Grand Challenge'.

Team 20 : IMMEDIAB: Immunity and Metabolism of Diabetes

Name of the supervisor: Nicolas Venteclef

THEMES OF THE TEAM

The team of N. Venteclef addresses highly relevant lines of research in the field of pathogenesis of Type 2 diabetes with specific regards to the immune-mediated mechanisms leading to adipose tissue or systemic inflammation and their long-term complications. The team made pivotal discoveries in the field of obesity and T2 diabetes and continues to pursue this line of research by exploiting cutting-edge methodologies, taking advantage of human samples provided by the clinicians of the Necker Hospital as well as of preclinical models of obesity and insulin-resistance.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Team not present in the previous mandate.

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

Staff Total	**19**
Staff scientists	1 DR, 3 CR
MCU/PU/PH	1 MCU, 3 PUPH, 1 MCUPH, 1 PHU
Technicians and engineers	3
Post-docs	3
Ph.D students	3

EVALUATION

Overall assessment of the team

The team has made outstanding contributions to the field of immune regulation of obesity and insulin resistance with high-profile publications documenting novel cellular and molecular connections between regulation of myeloid cell functions, inflammation, metabolism, obesity and type II diabetes. World-leading expertise and credibility in the field is fully demonstrated. Notably, the team has developed new multi-level data integration projects that could have strong translational impact leading to the identification of new biomarkers and predictors of complications in obesity and T2D.

Strengths and possibilities linked to the context

The team's strategy and experimental approaches are highly innovative, addressing in particular the epigenetic and transcriptomic regulation of obesity and type 2 diabetes. Recent findings on the transcriptional circuitry underlying monocyte and macrophage regulation and the role of IRF5 have opened up a new and original line of research, which is likely to further strengthen the teams' ability to secure funding and the collaborative network of the team. The research on the crosstalk between immunity and tissue-resident cells in liver and pancreatic islets is also highly relevant and original, having in particular having revealed an unanticipated heterogeneity of Kupfer cells by defining KC2 cells as specifically endowed with immunometabolic functions. In addition, the team is well focused on identifying possible biomarkers and predictors of disease and long-term complications in obesity and T2D, thus paving the way for new patents and strong interactions with the private sector.

Weaknesses and risks linked to the context

No major weakness.

Analysis of the team's trajectory

The Venteclef's team is highly multidisciplinary and has achieved significant results in basic research projects as well as in clinical trials involving the use/analysis of human samples and integration of research data with clinical data. This is well demonstrated by the ability to secure highly prestigious research funding (e.g., ERC Consolidator grant). The high quality of the research team and the multidisciplinary highly innovative approach will certainly lead the team to new lines of research, high-impact publications and significant funding.

RECOMMENDATIONS TO THE TEAM

The team should continue to exploit the multidisciplinary approach and integrate advanced bioinformatic expertise and a data manager in their team to effectively implement their multilevel data analysis.

Team 21 : Auto-immune and Immune B cells

Name of the supervisor: Matthieu Mahevas

THEMES OF THE TEAM

Research from the team is focused on the human humoral immune response and the conditions leading to protective response (against pathogens and vaccine antigens), long-term immune memory and eventually tolerance breakdown. The tolerance breakdown models studied include in particular autoimmune thrombocytopenia and the selective immune deficiencies resulting from anti-Type I IFN autoimmune responses.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Not applicable

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

Staff Total	**10**
Staff scientists	1 CR
MCU/PU/PH	1 PUPH
Technicians and engineers	1 permanent + 2
Post-docs	3
Ph.D students	2

EVALUATION

Overall assessment of the team

The team, formerly led by C-A Reynaud and J-C Weill, has excelled in human immunology, making major contributions to understand immunoglobulin gene diversification and B cell differentiation processes. M. Mahévas has introduced new research themes on human long-term memory B cells and tolerance breakdown. His outstanding scientific activity, highlighted by high-impact publications, tracks the generation of memory B cells post-SARS-CoV-2 infection and/or vaccination. The proposed innovative scientific program aligns with the team's expertise, is well-funded (ATIPE Avenir) and entirely feasible.

Strengths and possibilities linked to the context

The team has demonstrated its ability to conduct on the long-term ambitious programs and it has all the necessary expertise and methodology for state-of-the-art exploration of human immune response, including at the cellular, molecular, functional and single-cell level. Presence of Claude-Agnès Reynaud and Jean-Claude Weill in the team as emeritus professors constitutes an additional strength. The team has also demonstrated in the COVID period its ability to adapt and be innovative and productive even in a moving and unstable context. The team activity directly connects basic researchers with clinicians, which ensures the ability to translate results from basic research into a better understanding of human immune disorders and into the design of clinical trials. The team has established strong collaborations with other outstanding teams, notably at the Pasteur institute (F. Rey/ P. Bruhns) and Institut Imagine (F. Rieux-Laucat/ A. Fischer/ JL Casanova / L Abel).

Weaknesses and risks linked to the context

No major weakness

Analysis of the team's trajectory

The team first grew as a research group within one of the best immunology team in France with worldwide acknowledged expertise about B cell responses. The new Avenir team lead by Mathier Mahévas has recently demonstrated its ability to make high impact scientific contributions and to translate them into clinical trials. The projects are sound, innovative and fully feasible.

RECOMMENDATIONS TO THE TEAM

Secure tenure track positions for the young investigators of the team and attract new additional young investigators.

CONDUCT OF THE INTERVIEWS

Dates

Start: 22 janvier 2024 à 09h00

End: 23 janvier 2024 à 18h00

Interview conducted: on-site

INTERVIEW SCHEDULE

20 min presentation – 15 min Questions
Total time slots of 45 min / team to allow debrief.
Two presentation groups in parallel.
Proposition de 20 min presentation – 15 min Questions
Total time slots of 45 min / team to allow debrief.
Two presentation groups in parallel.
Day 1
8:45-9:00 Preliminary meeting of the experts committee
9:00-9 :15 Introduction: presentation program and HCERES experts committee
9:15-10:10 Presentation INEM by DU (40 min presentation + 15 min questions)
Group 1
AM
10:15-11:00 Team 3 Chatenoud Lucienne Leite Moraes Maria: Immunoregulation and Immunopathology.
11:00-11:15 Coffee break
11:15-12:00 Team 4 Fillatreau Simon: Immunity in Health and Disease.
12:00-12:45 Team 6 Morel Etienne: Autophagy, endomembranes & cellular dynamics in stress response
Group 2
AM
10:15-11:00 Team 5 Goffin Vincent: PRL/GH pathophysiology: translational approaches
11:00-11:15 Coffee break
11:15-12:00 Team 9 Pende Mario: Cell growth control by nutrients
12:00-12:45 Team 10 Pontoglio Marco: Epigenetics and development
12:45-14:00 Lunch
Group 1
PM
14:00-14:45 Team 13 Van Endert Peter: Innate and adaptive immune pathways in autoimmunity and autoinflammation (**in visio-conference**)
14:45-15:30 Team 7 Nassif Xavier Charbit Alain: Pathogenesis of systemic infections
15:30-16:15 Team 16 Manoury Benedicte: Immune response and Danger Signals
16:15-16:30 Coffee break
16:30-17:15 Team 18 Shapira Sagi: Laboratory of System Biology
17:15-18:00 Team 19 Vargas Pablo: Leukomotion Lab
Group 2
PM
14:00-14:45 Team 11 Sermet Isabelle: Cystic Fibrosis and other epithelial respiratory protein
14:45-15:30 Team 12 Terzi Fabiola: Mechanisms and therapeutic strategies of chronic kidney disease **15:30-16:15**
16:15-16:30 Coffee break
16:30-17:15 Team 14 Panasyuk Ganna: Mechanisms of nutrient sensing
17:15-18:00 Team 2 Asnafi Vahid Macintyre Elizabeth: Normal and pathological lymphoid differentiation
Day 2
Group 1
AM
9:00-9:45 Team 20 Venteclef Nicolas: IMMEDIAB: Immunity and Metabolism of Diabetes
9:45-10:30 Team 21 Mahevas Matthieu: Auto-immune and Immune B cells.
10:30-10:45 Coffee break
10:45-11:30 Team 1 Arbibe Laurence: Genome plasticity and infections.
11:30-12:15 Team 14 Schnupf Pamela: Host-microbiota interaction.
Group 2
AM
9:00-9:45 Team 15 Canaud Guillaume**:** Translational and Personalized Medicine Laboratory
9:45-10:30 Team 8 Oury Franck: Integrative Neurobiology
12:15-13:30 Lunch with "Tutelles"
The afternoon of Day 2 will be dedicated to other meetings with staff categories and deliberation

Group 1
13:30-14:00 Meeting PhD students
14:00-14:30 Meeting Post-docs
Group 2
13:30-14:00 Meeting Engineers / Technicians
14:00-14:30 Meeting Researchers
14:30-16:30 Meeting of the experts committee
16:30-16:45 Coffee break
16:45-17:45 Meeting with the DU
18:15 End of the meeting

PARTICULAR POINT TO BE MENTIONED

The evaluation committee praises INEM members for respecting the time of their intervention and the excellent organization of the visit.

GENERAL OBSERVATIONS OF THE SUPERVISORS

Université Paris Cité

Le Président

Paris, le 5 Avril 2024

HCERES
2 rue Albert Einstein
75013 Paris

Objet : Rapport d'évaluation de l'unité **DER-PUR250024174 - INEM - Institut Necker enfants malades - centre de recherche**.

Madame, Monsieur,

L'université Paris Cité (UPCité) a pris connaissance du rapport d'évaluation de l'unité INEM - Institut Necker enfants malades - centre de recherche.

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 des acteurs d'UPCité remercie le comité pour son travail d'évaluation.

Le doyen la Faculté de Santé et moi-même souhaitons souligner que l'Institut Necker Enfants Malades (INEM) est une unité reconnue par UPCité, l'INSERM et le CNRS. Cette unité se focalise sur les études physiopathologiques dans différents domaines comme certaines maladies chroniques, des dérégulations immunologiques ou des syndromes métaboliques. Adossée à l'hôpital Necker, l'unité couvre les domaines de la recherche fondamentale jusqu'aux études cliniques, incluant une forte activité de valorisation de la recherche. Elle est adossée à un scientific advisory board (SAB) international qui la conseille dans ses restructurations afin de converger vers une recherche remarquable. Son attractivité et son bilan sont exceptionnels (e.g., obtention de plusieurs ERC). L'unité est adossée à une unité de service / appui à la recherche qui regroupe l'ensemble des plateformes, qu'elle mutualise avec l'IHU Imagine. Cette unité a une reconnaissance nationale et internationale indiscutable et se positionne comme un fleuron de l'université.

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

Édouard Kaminski

Présidence

Référence
Pr/DGDRIVE/2023

Affaire suivie par
Christine Debydeal - DGDRIVE

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Institut Necker Enfants Malades

Directrice : Dr. Fabiola Terzi

Paris, le 29 mars 2024

To: HECRES Evaluation committee experts
Evaluation Campaign 2023-2024
GROUP D

Object: Evaluation report – INEM – general observations

Dear colleagues,

INEM would like to thank the experts of the evaluation committee for their insightful feedback. We value these recommendations as instrumental in our ongoing efforts to enhance our institute's operations and impact. Below, we provide some responses to points raised in the evaluation report.

Concerning the Institute

1. Department Structure and Organizational Dynamics

We acknowledge the recommendation to "*reassess our departmental structure and embrace a more dynamic organizational model*". As per this suggestion, we have initiated discussions on potentially restructuring our departments and establishing scientific axes to foster collaboration and innovation among teams. We are actively exploring the feasibility of holding common lab meetings for all institute members, as proposed during the evaluation committee's visit.

2. Enhanced Communication

Regarding the enhancement of communication, we wish to highlight our existing mechanisms, including two Laboratory Councils and two General Assemblies per year, facilitating discussions on both scientific and organizational aspects of the Institute. Additionally, since February, we have started regular dissemination (minutes mailing to all INEM members) of discussions and decisions from monthly PI meetings aligning with the committee's recommendation

3. Establishing INEM as a Distinct Research Brand

Recognizing the importance of strengthening INEM's identity within the Necker environment, we have undertaken proactive measures. These include collaborative efforts with the "Fondation Recherche Necker Enfants Malades" to develop an INEM brand. In parallel, from September 2023, we have recruited a dedicated communication officer to augment media coverage and revamp our website. The new website will be launched before summer. To increase our visibility, the evaluation committee experts also suggest to organize "*international conferences focusing on INEM specifics*". We fully agree on this point. In fact, since the creation of INEM, we have organized an INEM Symposium every two years (with a Covid break). The fourth symposium, dedicated to celebrate the 10th years of INEM, on "Molecular and cellular metabolism in health and disease" will be hosted at INEM the next November. Five members of INEM will present their researches.

4. Addressing Gender Bias and Recruiting Younger Team Leaders

We are attentive to concerns regarding gender bias among group leaders and the necessity of recruiting younger team leaders. While these factors are integral considerations in our recruitment processes, we acknowledge challenges in alignment with applicant qualifications. However, we are pleased to mention that among the upcoming three teams to be established in 2024, two will be directed by women, among whom, one is quite young (6 year after her PhD Defense).

5. Gender Equality Committee

Concerning the recommendation of "*establishing a Gender Equality Committee*", we are afraid that there is a misunderstanding. In fact, such committee has been already established at INEM since December 2022, underscoring our proactive stance on fostering gender equity within our institute.

6. Establishing an International PhD Program

Acknowledging the importance of an international PhD program in attracting talented students, we have initiated, since the last year, discussions with our Foundation to secure support for its establishment. A fund-raising campaign is ongoing to promote this program. Additionally, since the creation of INEM in 2014, we have been pro-active to participate in international doctoral training networks. In particular, we have hosted 8 European students in the context of the Doctoral Innovative training networks (ITN) Marie Sklodowska-Curie Actions. In addition, one of these programs, TrainCKDis, is coordinated by INEM (Fabiola Terzi).

7. Implementing a Bioinformatic Hub

We recognize the utmost importance of this matter for INEM, which prompted the recruitment of Sagi Shapira, a systems biologist, as group leader in 2022. Additionally, the establishment of an INEM Bioinformatics club and the successful application for a "Fédération de Recherche" on the "Paris Quantitative Biology Initiative" at CNRS in 2023 underline our commitment. Several INEM members are currently spearheading these initiatives. Simultaneously, we have opted to synergize with Imagine to advance Data Science and Artificial Intelligence endeavors on the Necker campus.

8. Improving Organizational Processes

We value the recommendations pertaining to organizational improvements, including updating the "réglement intérieur", reorganizing the "assistants de prevention", appointing a scientific integrity referent, and implementing a data management plan. We assure due consideration of all recommendations. Concerning the "réglement intérieur", it is important to clarify that, as discussed during the visit, we have been actively engaged in its update for the past six months. The revised version is scheduled for approval in June 2024.

9. Renewal of Permanent Technical Staff

Fully aligning with the observation on the need for renewing permanent technical staff, we are actively advocating for additional positions to support INEM's operational and research needs, recognizing the critical importance of continued support in this regard. However, as recognized by the evaluation committee experts, it is regrettable that this matter lies beyond our direct purview and is subject to the decisions of our governing bodies ("tutelles").

Concerning the teams

Team 1, Supervisor Laurence Arbibe

The report states that "The group of Laurence Arbibe should spend less time on the enterobacteria genotoxin project, which is much less competitive." The team leader respectfully disagrees with this statement. Contrary to this assessment, the project has garnered significant attention and is presently undergoing revision for potential publication in Nature Communications. The field of genotoxic enterobacteria is highly competitive on an international scale, with high impact factor publications over the past decade, particularly in the context of inflammatory bowel diseases (IBD) (DOI: 10.1126/science.abm3233). The team now has evidence that these genotoxic traits offer a substantial advantage for colonization by proinflammatory *E. coli* pathobionts in IBD. This justifies further investigations into the role of these toxins in contributing to inflammation and the genomic instability observed in IBD.

Team 5, Supervisor Vincent Goffin

We need to clarify that the statement provided is misleading: "*The head of the team is retiring within the next mandate. The new team leader has been identified but his research focus is mainly on breast cancer and not prostate cancer. The question related as to whether the other thematic (prostate cancer) will be maintained or not*". The accurate timeline is that the current head, aged 59, plans to retire in 2031, not during the upcoming mandate spanning 2025-2029.

Additionally, the report states that the "*new team leader is not identified*". During the discussion with the evaluation committee experts, it was emphasized that the current team hosts two promising tenure scientists, one researcher (breast cancer axis), and one clinician (prostate cancer axis). The future of the team beyond 2029 is starting to be discussed internally and will be considered according to INEM scientific policy for the 2030-2034 mandate.

Team 10, Supervisor Marco Pontoglio

The report states that "*There is a low capability within the team to perform bioinformatic analysis*". The team wonders if there might be a misunderstanding, given that the team is one of the few at INEM having a bioinformatic engineer since its creation. Furthermore, the team leader is also skilled in coding and bioinformatics.

The report also mentions that "*the identification of team leader succession is not clear*". During the discussion with the evaluation committee experts, it was emphasized the presence of a promising clinician within the team who could potentially succeed as the team leader.

Team 12, Supervisor Fabiola Terzi

The report states that "the *research activity could be more focused on translational clinical settings*". However, the team, comprising 9 clinicians, has published more that 350 translational clinical articles in the last mandate, rendering this recommendation inappropriate. The translation of the team's experimental findings to humans has led to the identification of several prognostic biomarkers as well as therapeutic targets, resulting in the filing of 10 patents in the last mandate.

Regarding the recommendation that "*the research team could boost dissemination by engaging scientific meetings, seminar and workshops*", the team members acknowledge that there is always room for improvement. However, it is important to note that the team members have presented their researches at over 100 meetings during the last mandate, most of which were international. Additionally, several team members have actively participated in dissemination though national media channels (newspaper, radio, TV), as outlined in the HCERES application.

We would like to thank again the evaluation committee experts for their thoughtful recommendations. We are confident that incorporating their input will significantly enhance the development of INEM.

Fabiola Terzi,
Directrice de l'INEM

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