Research evaluation

EVALUATION REPORT OF THE UNIT

HIPI - Immunologie Humaine, Physiopathologie & Immunothérapie

UNDER THE SUPERVISION OF THE FOLLOWING ESTABLISHMENTS AND ORGANISMS:

Université Paris Cité

Institut national de la santé et de la recherche médicale - Inserm

EVALUATION CAMPAIGN 2023-2024

GROUP D

Report published on March, 04 2024

High Council for evaluation of research and highter education

In the name of the expert committee :

Nabila Seddiki, chairwoman of the committee

For the Hcéres :

Stéphane Le Bouler, acting president

In accordance with articles R. 114-15 and R. 114-10 of the Research Code, the evaluation reports drawn up by the expert committees are signed by the chairmen of these committees and countersigned by the president of Hcéres.

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

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

MEMBERS OF THE EXPERT COMMITTEE

Chairperson:	Ms Nabila Seddiki, CEA, Fontenay-aux-Roses
Experts:	Ms Nathalie Bendriss-Vermare, Centre de Recherche en Cancérologie de Lyon Mr Andrea Cimarelli, CNRS, Lyon Ms Anne Jarry, Inserm, Nantes Ms Virginie Lafont, Inserm, Montpellier Mr Roland Liblau, Inserm, Toulouse (representative of CSS Inserm) Ms Marianne Mangeney, CNRS, Villejuif Ms Noushin Mossadegh-Keller, CNRS, Marseille (supporting personnel) Ms Emilie Narni-Mancinelli, Inserm, Marseille

HCÉRES REPRESENTATIVE

Ms Muriel Mercier-Bonin

REPRESENTATIVES OF SUPERVISING INSTITUTIONS AND BODIES

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Ms Claire de Marguerye, Inserm
Ms Patricia Renesto, Inserm
Mr Michel Vidal, Faculté de Santé, Université Paris Cité

Ms Sophie d'Ambrosio, CEA
Ms Simone Mergui, CEA

CHARACTERISATION OF THE UNIT

- Name: Immunologie Humaine, Physiopathologie & Immunothérapie
- Acronym: HIPI
- Label and number: UMR 976
- Composition of the executive team: Mr Jean-Christophe Bories (director) & Ms Sophie Caillat-Zucman (deputy director)

SCIENTIFIC PANELS OF THE UNIT

SVE Sciences du vivant et environnement
SVE4 Immunité, infection et immunothérapie

THEMES OF THE UNIT

The unit "Human Immunology, pathophysiology and Immunotherapies" (HIPI; UMR_S976) aims to decipher novel immunological mechanisms at the molecular, cellular and tissue levels, and to link them to the physiopathology and improved clinical management of various immune-related diseases. HIPI comprises eight Inserm teams, one Atip-Avenir and two CEA teams, consisting of 314 staff members, of which 121 hold permanent positions (distributed among professors, scientists and research supporting personnel). These eleven research teams have complementary expertise and facilitated interactions and synergy between researchers and clinicians who were previously scattered in separate Inserm units. In this respect, HIPI has provided an improved environment to establish and support collaborative interactions between basic researchers and clinicians. Three main scientific fields of research have been developed: oncoimmunology, immuno-inflammation and stem cells and immunity. Each of these axes is common to at least two teams.

HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

HIPI results from the fusion of two previous Inserm units (U976 and U1126) together with four other research teams that originated from three different Inserm or CEA units (U1160, U1149, U944 and CEA-DRF-SRHI). Altogether, HIPI includes eleven research teams, which are located in four buildings (Hayem, Bazin, Lallier and Meary), within the Saint-Louis Hospital campus. HIPI is one of the four research units affiliated to the 'Institut de Recherche Saint-Louis' (IRSL) at Saint-Louis Hospital in Paris. IRSL has been an important centre for research in immunology since its creation 60 years ago. It benefits from its close association with Saint-Louis Hospital, which is a major centre for the treatment of immune, haematological and skin disorders in Europe.

RESEARCH ENVIRONMENT OF THE UNIT

HIPI is a joint research laboratory of Université Paris Cité, Inserm and CEA. The unit has access to the IRSL's high-quality core facilities: microscopy, cytometry, genomics, and an L3 laboratory. HIPI teams are involved in several structuring programs, including 'Programme d'Investissement d'Avenir' (PIA 'Grand défi Bioproduction', PIA 'Maladies rares', PIA Inflamex); 'Initiative d'Excellence' (Idex Université Paris Cité, CD STROMA); 'Recherche Hospitalo-Universitaire' (RHU COVIFERON and iLite); 'Fédérations Hospitalo-Universitaires' (FHU APOLLO); 'Institut Hospitalo-Universitaire' (IHU THEMA).

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

Catégories de personnel	Effectifs
Professeurs et assimilés	38
Maitres de conférences et assimilés	15
Directeurs de recherche et assimilés	7
Chargés de recherche et assimilés	15
Personnels d'appui à la recherche	62
Sous-total personnels permanents en activité	**137**
Enseignants-chercheurs et chercheurs non permanents et assimilés	37
Personnels d'appui non permanents	9
Post-doctorants	19

Doctorants	85
Sous-total personnels non permanents en activité	**150**
Total personnels	**287**

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	32	1	6
Inserm	0	16	22
Autres	8	5	29
Total personnels	**40**	**22**	**57**

GLOBAL ASSESSMENT

The global performance of the HIPI unit is excellent.

During the reporting period (2017-2022), HIPI addressed previous recommendations by achieving excellent scientific production (>1500 publications), and amongst them >500 publications as first/last author published as highly original research articles in prestigious journals (e.g. Cell, Nat. Immunol., NEJM, Immunity, Blood, Nat. Commun., PNAS, JEM) in the fields of stem cell, cellular and molecular immunology, inflammation, cancer biology and treatment. The unit has hired two Inserm researchers ('chargés de recherche', CR) who have integrated two different teams (4 and 5) and will develop their research in complementarity with established HIPI's scientific objectives, and will show their potential to become leading scientists in the next mandate.

HIPI fosters intramural collaborations and has established strong collaborative networks between researchers and clinicians. Valuable sample repositories have been implemented for the development of a strong scientific program based on fundamental and translational research towards innovative therapies. HIPI develops innovative research and technologies including CAR-T/CAR-MAIT cell, bioprinting of tissues/organoids or physics of the cytoskeleton and morphogenesis amongst others, and fosters innovation through industrial partnerships in the fields of immunology, oncology and biotherapies.

HIPI's research activities are guaranteed by outstanding funding secured from national and international public and private funding bodies (>10.5 M€ with HIPI team members as PI for most of them, including 2 European Research Council grants, 5 PHRC, 16 ANR grants, 10 INCa grants and 9 PIA grants). HIPI is supported by state-of-the-art technological platforms, including high-level imaging technology, that are valued by all personnel and scientific staff interested in fundamental and translational haemato-onco-immunology and inflammation.

Several HIPI teams have established connections to the socio-economic world, including the filing of 39 patents and the establishment of productive partnerships with the industrial sector. These achievements include an anti-KIR3DL2 therapeutic antibody tested in the phase I/II clinical trial "Proof-of-concept for its use in "Sézary syndrome", the use of STAT inhibitors in Kit-mutated melanoma or new discoveries on hematopoietic stem cells differentiation for the treatment of some haematological malignancies. Altogether, HIPI's innovations led to the creation of four start-up and biotech-companies.

HIPI remains an excellent centre for doctoral training (66 PhD thesis defence). With its partnership with Université Paris Cité, HIPI provides teaching opportunities within integrated programs at Master and PhD levels (Doctoral Schools HOB, BioSPC, and CBMS) and development of interdisciplinary research. HIPI members have strong name recognition in their respective fields of interest, receiving invitations as speakers to international meetings (ESDR, EORTC, EAOD, AACR), organizing international meetings (e.g., International Conference on HLA-G; Congrès international d'ORL pédiatrique), participating to editorial boards of peer-reviewed scientific journals (e.g., Translational Oncology, American Journal of Cancer Research) contributing to science assessment as scientific members of national and international funding bodies (e.g., Ligue Nationale contre le Cancer, Inserm, Organisation européenne de biologie moléculaire (EMBO)), and receiving prizes for their contributions to science (e.g., Prix Jean Bernard (FRM); Prix Sezary de l'Académie Nationale de Médecine; Prix de Médecine de la Chancellerie des Universités).
Currently, HIPI is facing a substantial restructuring of its teams, which has started and will continue throughout 2024 with the creation of the Saint-Louis research Institute 2025-2029. The new multi-disciplinary unit will result from the fusion of several structures including virology, cell therapy, cell biology and data science disciplines.

Four teams are departing from HIPI (retiring or relocating to other structures) and other teams are restructuring with new teams joining and new CR permanent positions created. To what extent the reshuffling of the different teams will impact on the careers and projects of post-docs, graduate students, engineers and technicians is presently difficult to estimate, and represents an important aspect of the future unit's life and scientific output. The new scientific direction will need to assess this with great care. In support of this, a higher transparency of the decision-making processes and improvement of top-down communication to the personnel (researchers including students, engineers, and technicians), as well as a structured and formalized bottom-up advising process regarding strategic and unit life issues, are encouraged. Also, the student association of IRSL, ADELIS, should provide a social interaction network for PhD students/post-docs and thus needs to be reactivated. Revising and optimizing the administrative support at HIPI for the planning of suitable career paths and offering a stronger visibility to, and care for lab personnel needs is expected to improve the unit's spirit. The future direction is also strongly encouraged to continue requesting support from legal entities (Inserm and University) for refurbishment of premises in compliance with hygiene and safety standards, thereby contributing to the collective well-being.

DETAILED EVALUATION OF THE UNIT

A - CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

1. Recommendations on scientific production and activities - The teams should strive to improve the level of publication in high impact journals and strive to increase the amount of citations.

The research programs carried out by HIPI teams allowed the publication of several papers in high-impact journals such as Cell, Immunity, Nat. Immunol., Nat. Cell Biol., Nat. Commun., JEM, EMBO J. or PNAS. The contributions to these notorious journals will certainly increase the visibility of HIPI.

2. Recommendations on the unit's organization and life - a) Increase internal communication between teams: HIPI needs to organize regular internal workshops, seminars, and retreats.

HIPI's scientists meet at weekly internal seminars and monthly seminars, gathering researchers and clinicians. Invitation of top scientists for on-site talks are regularly organized. The unit has also organized retreats for the team leaders where scientific and strategic issues were discussed.

b) Need to stabilize permanent positions for young scientists:

The unit has recruited 2 young Inserm researchers for Teams 5 and 4. An Atip-Avenir team has also joined HIPI to strengthen basic research on human cancers and infectious diseases.

c) Bio-informaticians need to join HIPI for data analysis.

One permanent position for an Inserm bio-informatics engineer is expected in 2023.

d) Funds should be available for travelling to international meetings for the young researchers and PhD students. There is still no specific fund from HIPI that has been dedicated for students/post-docs travelling to international meetings. However, part of the funding provided by the supervisory authorities is re-allocated to each team to cover this kind of expenses.

e) To establish more links between immunology and cell biology.

This aspect has not been clearly addressed. More efforts towards this are planned in the future centre.

f) The directors should be aware that the coming period will require strong and adapted management to secure the common budget for the technological platforms and to further favor interdisciplinary projects.

This aspect has not been clearly addressed. The future direction will be careful regarding this point in the next mandate.

3. Recommendations on scientific strategy and projects - *To strengthen collaborative work between teams and invest in new research strategies based on unique expertise in immunology and hematology present within HIPI.*

Collaboration between teams has been a priority and several common projects were developed and, for some of them, completed and published. For example, Teams 1, 2 and 4 have explored the role of regulatory T cells in Human Chronic Graft-Versus-Host Disease. Similarly, a tight cooperation between Teams 1 and 5 has led to the development of novel therapeutic tools in myeloma and cutaneous T-cell lymphomas. Furthermore, Teams 2 and 9 shared expertise to explore dynamic changes in T-cells in the context of dupilumab treatment of atopic dermatitis. Thus, the creation of the HIPI unit has efficiently strengthened the collaboration between teams around common goals of translational research.

B - EVALUATION AREAS

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

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

Assessment on the scientific objectives of the unit

The scientific objectives of the unit are excellent. HIPI structure is in the right environment at Saint-Louis Hospital, which is an ideal place for scientists and clinicians to interact, and the resulting collaborations are excellent.

Assessment on the unit's resources

HIPI scientists have access to excellent to outstanding resources, including funding, valuable sample repositories and efficient interaction with clinical departments providing opportunities for translational research/interaction with private companies, excellent technological platforms and implication in undergraduate programs of Université Paris Cité, thus attracting students.

Assessment on the functioning of the unit

Despite the major efforts made by the current direction, HIPI's functioning, notably working conditions due to old premises and suboptimal internal communication, remains fair and has not been facilitated by recurrent changes in the last mandate with 3 different directors.

1/ The unit has set itself relevant scientific objectives.

Strengths and possibilities linked to the context

HIPI general scientific objectives are to decipher novel immunological mechanisms at the molecular and cellular levels, and link them to the pathophysiology of immune related disorders to improve their clinical management. There is undoubtedly a strong potential within HIPI to reach these goals given the tight links between researchers and the clinical departments of the hospital, which are leaders in medical oncology, Immuno-haematology, hematopoietic stem cell transplantation, renal transplantation, onco-dermatology, inflammatory skin diseases and urology (about half of the team leaders are physician-scientists). Clear primary and interconnected research axes, with the immune system as a central pillar, have been established to decipher mechanisms in oncoimmunology, immuno-inflammation, stem cells and immunity. Indeed, HIPI is an appropriate research structure in the right environment with an access to large cohorts of patients and biological samples, to test and discover new immunotherapies.

Other important research axes, which are interconnected with the former ones and highly considered by HIPI teams, focus on inflammatory processes and regulatory mechanisms that lead to skin diseases and allograft acceptance, respectively. Various immune reactions are central to the rejection of kidney, lung or liver transplantation, as well as in allogeneic hematopoietic stem cell transplantation. HIPI teams aim to use cutting-edge technologies, including high-dimensional technologies such as metabolome, single-cell transcriptome and multi-parameter flow cytometry to investigate both tumour and immune cells in order to identify new therapeutic targets, with a particular focus on urologic and breast cancers, melanoma, multiple myeloma and lymphoma. Indeed, better characterization of immunological/inflammatory networks could contribute to the development of novel therapeutic strategies.

Weaknesses and risks linked to the context

While HIPI scientific objectives and feasibility are supported by the access to clinical resources, i.e. expertise, patients' cohorts and samples, the technological platforms and bioinformatics analytic capacity seem undersized in terms of manpower and expertise. Indeed, productivity and discoveries would undoubtedly increase provided that the HIPI management team would invest in this direction.

Across team collaborations, the pipelines and strategies that will strengthen such collaborations are not clearly presented.

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

HIPI has set itself several missions: basic, translational and clinical research, education, industry partnership and academic collaboration.

Amongst the 11 HIPI teams, about 50% are directed by full-time researchers. Most teams have few (1 to 4) tenured scientists and between 4 and 11 permanent scientists (PU-PH, MCU-PH, MCU, DR, CR); the technical support (IR, IE) is fairly evenly attributed to small and larger teams. Also, there are quite a large number of non-permanent researchers and engineers/technicians in many teams, thus contributing to research productivity.

HIPI succeeded in developing ambitious work programs ranging from basic immunology to translational and clinical research. To cover these research developments, several types of financial resources have been raised during the reporting period, to reach a total of more than 29 M€.

Recurrent resources are allocated by supervisory bodies for a total of 400 k€ per year (Inserm: 219 k€ per year and University from 130 to 185 k€ per year). The main part of this funding is re-allocated to each team, in proportion to its size (number of researchers). A smaller part of the resources, around 15-20% over the period, is dedicated to common expenses (acquisition of new equipment, web site, infrastructure, organization of seminars, etc.), as well as to help young team leaders (e.g. Atip-Avenir group) to start their own research.

Weaknesses and risks linked to the context

Given the high number of teaching staff, HIPI members (MCU/MCU-PH) should apply to the Université Paris Cité "Chair of Excellence" for positions/opportunities if any. This is expected to give more time for lecturers/teachers to interact with students, post-docs, technicians, and engineers.

The number of PhD students and post-docs is not well balanced between the different teams despite the presence of a fair number of HDR holders.

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

PhD students are closely supervised by their scientific directors who typically organize weekly meetings. Bi-monthly meetings gathering all team members are organized to discuss scientific and technical matters. Similarly, unit seminars are held once a week to favour exchanges and collaborations between HIPI teams.

Most of HIPI teams (e.g. 1, 3 and 5) comply with gender equality in accordance with institutional rules of the employers at Inserm and Université Paris Cité.

Inserm laboratory notebooks are used by all teams. Electronic lab books have been proposed to all unit members and ensure a good traceability of the data.

Weaknesses and risks linked to the context

The very poor working conditions in the unit, due to old premises, need to be improved.

HIPI has not yet appointed an international/national Scientific Advisory Board that can meet regularly to discuss the strategy of the unit and implement it into its research vision and networking activity.

The decision-making processes suffer from a lack of transparency. Likewise, there is room for improvement of top-down communication to the personnel (researchers including students/post-docs, engineers, and technicians), as well as of the bottom-up advising process regarding the strategic and unit life decisions.

A student association, ADELIS, which provides a social interaction network for PhD students has been created, but needs to be reactivated.

There is room for revising and optimizing the administrative support at HIPI for the planning of suitable career paths and offering a stronger visibility to, and care for lab personnel needs. This is important to improve the unit's collective spirit.

The engagement of the unit in sustainable development (i.e. by encouraging recycling and bike transportation by providing parking, repair services and bins for paper, plastics, tip box recycling) is not clearly assessed.

EVALUATION AREA 2: ATTRACTIVENESS

Assessment on the attractiveness of the unit

The attractiveness of the unit is very good to excellent. With its partnership with Université Paris Cité, HIPI provides doctoral training (88 PhD students), teaching opportunities within integrated programs at Master and PhD levels. However, international post-docs attractiveness remains average and some researchers have moved and are no longer part of the unit.

HIPI members have strong name recognition in their respective fields of interest, receiving invitations as speakers to international meetings (ESDR, EORTC, EAOD, AACR), participating to editorial boards of peer-reviewed scientific journals, and securing excellent fund raising (2 ERC, 5 PHRC, 16 ANR, 10 INCa and 9 PIA grants).

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

During the reporting period, team leaders and staff-scientists of HIPI participated to the organisation of 12 international symposia and conferences (e.g. 'Congrès international d'ORL pédiatrique Dialogues 2018', EADO 2019, EORTC Cutaneous Lymphoma Group Meeting 2021, "Congrès annuel de recherche dermatologique", International Conference on HLA-G). Furthermore, HIPI members were invited to talk in more than 55 meetings, such as the American Society of Hematology (more than 20 talks from Teams 4 and 5), the International Keloid Symposium, the World Congress in Foetal Medicine or the European Society for Blood and Marrow Transplantation. Webinar presentations such as the 5th Disease Maps Community Meeting or the American Association of Paediatric Otolaryngologist have also been organised. The unit also encouraged doctoral and post-doctoral researchers to attend and present their research at national and international meetings. Part of the funding provided by the supervisory authorities and re-allocated to each team was used to cover these expenses.

HIPI members hold editorial responsibilities in scientific journals, in scientific expertise bodies in France and abroad (e.g. ARC, ERC, Inserm, Hcéres), and are elected or appointed members of national and/or international scientific academies (e.g. 'Groupe d'Études des Tumeurs Uro-Génitales', 'Centre Intégré de Cancérologie du Groupe Hospitalier Saint-Louis Lariboisière', 'Direction de l'Organisation Médicale et des relations avec l'Université (DOMU) de l'AP-HP', 'Association Oncodéfi', 'Unité de Coordination en Onco-Gériatrie (UCOG) Paris – Nord', 'Société Française d'Oncologie Médicale', 'Comité scientifique du congrès de la Société française de Radiothérapie Oncologie').

More than 20 HIPI members were laureates of prestigious prizes/distinctions (e.g. Prix Gallien France, Prix Sezary, Grand prix Robert Debré, Prix Jean Bernard (FRM)). Other prizes include Prix Victor et Erminia Mescle- FRM (2019), Prix Brigitte MERAND jeunes chercheurs Force Hemato (2022), Prix de Médecine de la Chancellerie des Universités (2022), Prix de la recherche Laurette Fugain (2022).

HIPI has directed constant effort towards recruiting junior and senior researchers. The number of staff scientists in the teams increased, through successful applications (i.e. Teams 4 and 5) for a permanent research position at Inserm. HIPI also attracted new teams through specific calls and by offering attractive packages in terms of both equipment and lab space, which led to the recruitment of the Atip-Avenir team in 2022.

The work of team members in teaching of various medical and scientific courses as well as giving talks at international and national congresses draws the attention of young scientists. During the reporting period, HIPI welcomed a total of 88 PhD students, 40 post-docs and 4 technicians with scientific or medical backgrounds.

Most junior researchers (including around 1/3 of international fellows) were awarded competitive grants (e.g., ERC, PHRC, PIA).

HIPI has developed an ambitious policy for responding to international or national calls. Each team is free to apply for international or national calls for projects, and when possible, several teams associate to apply for large calls, such as RHU, or to acquire common equipment. Thanks to this policy, team members have been successful in getting major competitive funding, including three European grants (1 ERC: 2 100 k€, 1 H2020: 1 267 k€, 1 IMI: 628 k€) (all as PI), five PHRC (all as PI for 2.9 M€), sixteen ANR grants (including 8 as PI for a total of 3.2 M€), ten INCa grants (for a total of 1.3 M€), nine PIA grants (RHU, Idex…), including three as PI for 3.78 M€, and 149 research contracts from associations or foundations (FRM, FdF, ARC…) for around 4.1 M€. The total resources obtained from competitive calls reached 24 M€. Overall, the strategy to raise research funds has been very successful.

Research, teaching and training bodies also benefit from many fellowship funding opportunities, provided, among others, by the IHU-B THEMA, the Institut Carnot OPALE, the SIRIC InsiTu, the Doctoral School Hematology-Oncogenesis-Biotherapies (HOB), and the Graduate school Innovative Therapies in Cancerology.

HIPI has developed and acquired its major equipment in the context of the technologic platforms of IRSL, which are organized into a dedicated technological unit (UMS Saint-Louis US53 / UAR2030). This facility, which includes cell sorters and cytometers, DNA sequencer, and confocal microscopes, is managed by dedicated engineers and is accessible to all unit members after appropriate training. The acquisition of new equipment has mainly been achieved through competitive calls, which associate most of the units of the Institute (Cancéropole, Idex…). Overall, the strategy of the unit is to cooperate with other units of the IRSL to acquire and maintain high quality equipment. This organization ensures an easy access to cutting edge technology and devices.

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

There is room for additional international grants, such as EU grants, that can help HIPI teams gain international recognition in addition to strengthening research means.

Many technical/engineer staff do not hold a permanent position and it is not clear what is the strategy and policy to secure their know-how in the unit. The strategy to hire and increase personnel dedicated to the platform with a vision to increase interactions with researchers will help increase internal interactions and multi-disciplinary collaborations.

There is a lack of trained permanent bioinformatics staff.

EVALUATION AREA 3: SCIENTIFIC PRODUCTION

Assessment on the scientific production of the unit

The scientific production of the unit is excellent with >1 500 publications, although non-homogeneously distributed within the different teams. Amongst them, >500 publications are as first/last author published as highly original research articles in prestigious journals (e.g. Cell, Nat. Immunol., NEJM, Immunity, Blood, Nat. Commun., PNAS, JEM). Collectively, this work has provided new and important findings in the domains of basic immunology, oncoimmunology, immuno-dermatology, immuno-haematology and stem cell biology. This will be continued with the recruitment of young scientists supported by HIPI direction.

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

All senior scientists have contributed to scientific publications that have led to new and important findings in the domains of basic immunology, oncoimmunology, immuno-dermatology, immuno-haematology and stem cell biology. The scientific production by members of the unit includes more than 1 500 original publications (>500 as first or last author), with some papers published in high-level international journals. For example, Team 1 reported the proof-of-concept for the use of a novel antibody in the treatment of patients with Sézary syndrome (Lancet Oncol. 2019) and the development of new drugs for melanoma (J. Invest. Dermatol. 2018). Team 2 discovered key mechanisms involved in inflammation and immune regulation in skin diseases (Nat. Commun. 2020 & PNAS 2019). Team 3 studied the source of antigenic peptides for the major histocompatibility class I pathway, and showed that these are derived from translation of pre-mRNAs and generate immune tolerance (PNAS 2023). Team 4 explored the mechanisms involved in acute GVHD. They demonstrated significant variation in microbiota-derived metabolites (Nat. Commun. 2019). Their work also demonstrated that MAIT cells have no alloreactive potential and are unable to induce GVHD tissue lesions, a result that suggested promising therapeutic potential for this unconventional T cell subset (J. Exp. Med. 2018). Results from Team 5 shed new light on how human adaptive immunity is established and maintained throughout human ontogeny (Immunity 2017). They revealed novel epigenetic regulation processes involved in the growth and genomic stability of Multiple Myeloma cells (PNAS 2017 and Leukemia 2021). Analysis of stem cells was extended towards applications in regenerative medicine. Team 6, with its multi-disciplinary expertise, combines clinical and basic research in breast cancer based on the strong link with the 'Senopôle' (Saint-Louis Hospital) and skills in molecular and cellular biology, immunological approaches and extracellular vesicles (EV) engineering (Scientific Reports 2020). Team 7 published the proof of concept for the use of human embryonic stem cell-derived cardiovascular progenitors in patients with severe ischemic left ventricular dysfunction (J. Am. Coll. Cardiol. 2018). The biophysical properties of human haematopoietic stem cells (HSC) were also analysed. Team 8 demonstrated that the force exerted by the microtubule network reorganizes the chromatin architecture and induces myeloid rather than lymphoid differentiation (EMBO J. 2020). Their work further revealed that stem cells can attach to certain stromal cells and become polarized when their centrosome is positioned against the contact point. This type of polarization is central to the function of B and T cells when interacting with antigens or killing target cells (J. Cell Biol., 2021). Team 9 investigated human immune cell communication through a combination of experimental and computational approaches. They developed ICELLNET, a computational framework to infer cell-cell communication from single cell or bulk cell transcriptomic data (Nat. Commun. 2021). Using a "systems approach" they established a multivariate mathematical model of cell-cell communication, using dendritic cells (DC) and T cells as a model (Cell 2019). T cell functions were also investigated in the context of cancers. Team 10 explored tumour-infiltrating T cell subpopulations and their responses to checkpoints (Cancer Immunol. Res. 2019). Their results support the therapeutic potential of targeting the HLA-G/ILT2 checkpoint in HLA-G+ tumours. Altogether, during the reporting period, HIPI team members have published major papers as corresponding authors in journals such as Cell (1); Immunity (1); Nat. Immunol. (2); Nat. Cell Biol. (1); Nat. Commun. (4); JEM (2); EMBO J (4); PNAS (3); Lancet Oncol. (1).

HIPI adheres strongly to the principles of scientific integrity, ethics and open science. Studies involving human materials and animals are conducted in agreement with the European rules and regulations and all protocols are approved by authorized Ethics Committees. The datasets generated during studies, including metabolomic, transcriptomic, microbiome, as well as high-dimensional cytometry datasets, are deposited in public repositories. All these raw data are accessible to the scientific community. Publications are internally reviewed by the team's PIs and when possible are also sent to external colleagues for cross-checking prior to submission. Documents, including these, are verified for plagiarism with the Compilatio software. In most cases, PhD students sign their papers as first author, and co-authors are decided according to the work accomplished. At least one publication per PhD student (as requested by the Doctoral School) or post-doc as first author, is produced.

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

It is worth underlining the quite variable number of articles and international presentations by the different teams. No committee for scientific integrity is yet in place within the unit for solving any potential arising issues.

EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

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

Integration of HIPI research activities in society is outstanding. HIPI works towards reinforcing the collaborations between basic scientists and clinicians in order to foster innovation through industrial partnerships in the fields of immunology oncology and biotherapies (39 patents). HIPI teams have established solid and highly productive links with the socio-economic world and/or industrial partners (creation of 4 start-up (Astraveus and Immunovadis)) and biotech-companies). HIPI team members actively participate to the dissemination of their scientific achievements to the general public.

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

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

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

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

The unit has established strong collaborations with numerous socio-economic partners. Interactions with pharma are highlighted by the funding of seven Cifre grants for doctoral students, including collaborations with Invectys, Servier or Complutense University of Madrid. Collaborations with socio-economic partners were established in order to support research and data analysis in the fields of immuno-hematology, skin diseases, and oncology. For example, partnerships were developed for the pre-clinical or clinical testing of novel therapeutic antibodies (e.g. anti-KIR3DL2/Innate Pharma; anti-CCR4/Kyowa Kirin or CYT-338/Cytovia Therapeutics), as well as of chemical reagents (e.g. PD-0332991/Pfizer). Overall, more than 40 contracts have been signed with pharma for a total amount of 5.4 M€.

HIPI was strongly committing to the valorisation of research activities and providing recommendations to national bodies. Several patents in various scientific themes of the unit have been published, including immune therapies, methods for producing therapeutic cells and data analysis. Specifically, Team 1 filed twenty patents (or applications) with Inserm Transfert for the identification of new tumour antigens as diagnostic, prognostic or therapeutic targets, as well as for the development of therapeutic antibodies or molecules, or the generation of murine models. Team 2 filed four patents related to the production of therapeutic regulatory T-cells. Team 4 filed two patents related to the production of therapeutic Mucosal-Associated Invariant T (MAIT) cells expressing Chimeric Antigen Receptors and one for a method for determining and improving the potential efficacy of anticancer treatment. Team 5 had two patents for novel Bispecific-T cell engager and CAR-T cells for Multiple Myeloma. Team 6 invented processes related to cancer treatments. Team 7 invented a microfluidic device, which includes a flow-regulating chamber and methods for generating cardiac progenitor cells for clinical use from primate embryonic stem cells, and their application. Team 10 patented novel T cells for diagnosis, prognosis or treatment of various diseases or cancers. Overall, HIPI has developed an active policy of innovation, which led to the production of more than 35 patents (or applications) during the reporting period, some of which have been licensed to pharma (Innate Pharma and Cytovia Therapeutics). In addition, three of these patents supported the creation of two start-ups (Alderaan Biotechnology, Jalon Therapeutics) and were licensed to these companies thereafter. Similarly, members of the unit have created biotech companies such as MadeCell (Team 8) and Quidditas Therapeutics (Team 8).

Members of the unit participated in or organized specific events aiming to share knowledge with the general public. Several HIPI's scientists, as members of the board of the French Club of Young Immunologists (FCYI, under the auspices of the French Society of Immunology (SFI)), (i) participated in the "Day of Immunology 2021" by creating a presentation aid to visit elementary school and discuss with children about the immune system, microbes and vaccines, (ii) coordinated an open call ('Ambassadeurs de l'Immunologie') through SFI to encourage researchers and clinicians to participate in this initiative, and (iii) participated in the 'Apprentis Chercheurs' initiative. Most teams participated in the program 'l'arbre des connaissances' that promotes the immersion of high school students in research labs. Team members also participated in symposia for patients organized by the patients' association Ellye ('Ensemble Leucémie Lymphomes Espoir') or I3M (for Multiple Myeloma). HIPI organized events for the general public in particular for school populations, such as 'la Fête de la Science'.

Societal engagement and work dissemination were also achieved through interactions with the general media, including TV news ('Envoyé Special' 'Magazine de la Santé', 'Allo docteur', etc.) or magazines/newspapers (e.g. L'express, Le Figaro, Le Monde, Le Nouvel Observateur).

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

None identified.

ANALYSIS OF THE UNIT'S TRAJECTORY

For the next few years, the heads of the existing teams, together with an ongoing plan initiated by the supervising bodies, have come with the decision to merge all the existing research units from the site of Saint-Louis into a single Institute referred to as "the Centre de Recherche Saint-Louis". The new UMR will keep its identity with respect to the scientific strengths of the existing teams. The principles of the governance and the organization of the teams are being refined and will be ready by mid-2024.

The mandate of the current IRSL director ends in December 2024. The anticipated 2025-2029 director will be supported by an executive board of co-directors emanating from the existing teams, an administrative staff, an international SAB and internal councils, with the mission to launch the research centre in January 2025 and establish the new scientific trajectory. At mid-term, an ad-hoc international committee will choose the subsequent director through an international call and high-ranking standards.

HIPI teams will be organized in nine teams instead of ten, as the team "Physics of the Cytoskeleton and Morphogenesis" moved to a different institute and will not participate in the future unit. For IRSL, the current organization within the Department of the 'UFR de Médecine' includes five Inserm research units (1 Inserm/CNRS), one UP EA and one UMS. The future unit will gather around 100 permanent agents, including 27 full-time researchers, 39 teachers-researchers and 28 engineers and technicians. Two new PIs with complementary expertise in oncoimmunology will join the unit and there will be a new leadership for some of the teams whose current leaders are retiring. The unit will continue focusing on translational clinical research and benefitting from close interactions between basic scientists and clinicians from the departments of medical oncology, dermatology, urology, immuno-haematology, hematopoietic stem cell transplantation and renal transplantation.

Basic research scientific objectives will rely on continuous and successful expertise on the differentiation and the function of lymphocytes (mainly B, T, MAIT and NK cells), the development of next generation immune-therapies for haematological malignancies and skin cancers, transplantation and novel processes of immune tolerance, the pathophysiology of skin, breast and urologic cancers and the evaluation of novel biotherapies.

Scientific objectives are in line with the previous program, which includes different axes:

Hematology: is a very strong axis in HIPI's interest as some of the teams have a long-term interest in malignant haematology, especially acute leukemia (AML and ALL), myelodysplastic syndromes, myeloproliferative disorders, bone marrow failure and preleukemia conditions such as Fanconi anemia and DDX41. These topics foster basic (hematopoiesis, oncogenesis) or translational research, preclinical studies, and conventional or innovative therapies (targeted therapies on vulnerabilities, cell therapies).

Immunology: is central in HIPI's work and links different axes. It relies on both basic and translational research thanks to the strong collaboration between researchers and clinicians from the different departments on site. This axis encompasses translational projects in transplantation and immune tolerance, adaptive immunity in cancer, inflammatory & infectious diseases and immunotherapy.

Dermatology and Oncology: This axis develops fundamental and translational research in the field of inflammatory, fibrosing and tumour cutaneous diseases, and breast cancers. Projects will be mainly focused on how to modulate the immune system to improve anti-tumour responses. New anti-tumour or anti-inflammatory therapeutic strategies (antibodies, peptides, inhibitors, engineered micro-vesicles, cell-based therapy) will be studied, as well as biomarkers predicting response or resistance to treatment. This axis will benefit from the strong and complementary expertise of the teams' members in cellular biology, immunology and genetics, reinforced by a long-lasting collaboration with the pathology, tumour genomic, breast cancer and dermatology departments of Saint-Louis Hospital.

Cell biology, Virology, Cell Therapy: This axis will address the cellular responses to genotoxic or viral stresses, contributing to basic and translational research and aiming at identifying the host cellular pathways, which determine the susceptibility to human viral diseases. Deciphering the underlying molecular and cellular mechanisms will be key to reveal new targets for future design of antiviral strategies. Viruses responsible for life-threatening infections in humans such as emerging viruses (respiratory viruses, arboviruses) and viruses that cause severe disease in immunocompromised patients (for instance HIV, BKV) will be investigated.

Data Science & Cohorts: The data science team will be central for designing prospective trials and for data analysis. This team will be multidisciplinary, including biostatisticians, clinicians, and biologists, actively collaborating, and interacting to provide the best answers to HIPI's scientific objectives. This team will liaise with all HIPI members for anticipating needs for data science program. Academic clinical research will take advantage of the various high-value, prospective, and fully annotated patient cohorts coordinated at Saint-Louis by the clinical key opinion leaders in the frame of the IHU-B THEMA, the national references centres for rare diseases, or the national disease-oriented cooperative groups.

The future scientific program will rely on the technological core facilities offering access to pre-clinical investigation on murine models as well as state-of-the-art imaging and flow cytometry technologies, and to additional supporting approaches in genomics and data analysis, A "Centre d'Investigation Clinique" for early therapeutic phases in cancerology will help HIPI reach scientific objectives of the future program.

HIPI's research, education and training programs will benefit from scholarship funding including those from the IHU-B THEMA, the Institut Carnot OPALE, the SIRIC InsiTu, the Doctoral School Haematology-Oncogenesis-Biotherapies (HOB), and the Graduate school Innovative Therapies in Cancerology.

The proposed scientific program has strong potential for clinical applications, which should foster industrial partnerships, as well as contributing to education and training of young researchers.

RECOMMENDATIONS TO THE UNIT

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

The committee encourages HIPI to maintain a higher transparency and involvement of different staff members in its decision-making process and improvement of top-down communication to the personnel (researchers including students/post-docs, engineers, and technicians), which will certainly help improve HIPI's functioning and the unit's spirit.

The unit should plan ahead and discuss with the students and post-docs and also ITA staff when teams are closing and staff members are to be redistributed to other teams. The new direction should favour communication and dialog in order to prevent any potential issue with and between all HIPI members.

The future direction is strongly encouraged to continue requesting support from legal entities (Inserm and University). Refurbishment of premises in compliance with hygiene and safety standards needs to be prioritized for the collective well-being.

The unit should also reinforce support for personal career development plans, notably, the yearly evaluation and promotion of engineers/technicians, and of the permanent and non-permanent staff including post-docs. A better organization of the bio-banking and data storage by implementing a biological resource centre and securing sufficient space capacity for bioinformatics data storage with dedicated management staff, will be an asset for favouring research developments.

The committee encourages the unit to appoint a Scientific Advisory Board with national and international experts that can meet on a regular basis to discuss the strategy of the unit in terms of research, vision and networking activity.

Recommendations regarding the Evaluation Area 2: Attractiveness

The committee encourages HIPI to work towards attracting international and national post-docs. The student association of IRSL, ADELIS, for providing a social interaction network for PhD students/post-docs needs to be reactivated.

The unit should continue recruiting and supporting young scientists. This support needs to be provided at all levels in order to keep up with this level and even more.

The optimization of the administrative support for career paths and increased wages will help towards reaching better attractiveness.

The committee highly encourages HIPI to continue with the outstanding fundraising capabilities and to increase grant submission at the European level.

Recommendations regarding Evaluation Area 3: Scientific Production

The unit should keep up with its excellent scientific productivity.

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

The unit should keep up with its outstanding research activities in society. It could strengthen these activities by asking students to get more involved in events for the general public. This is another way to improve the unit's spirit and cohesion.

TEAM-BY-TEAM OR THEME ASSESSMENT

Team 1: Onco-dermatology and Therapies

Name of the supervisor: Ms Anne Marie-Cardine

THEMES OF THE TEAM

The team develops ambitious research projects on skin cancers, mainly cutaneous T cell lymphoma (CTLC) and melanoma, which aim at i) identifying diagnostic and prognostic biomarkers; ii) identifying novel therapeutic targets; iii) testing new therapeutic approaches at the preclinical and clinical levels; and iv) deciphering the mechanisms of escape to currently available treatments.

The team, composed of researchers and clinicians with complementary expertise, develops translational research that has allowed identification of new therapeutic targets and generating proof of concepts for innovative treatments.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Most of the recommendations in the previous report have been considered.

1) The team should continue strive to improve its level of publication in high impact journals.

Members of the team have recently published as first, last and/or corresponding author in high-standard journals (Lancet Oncol. 2019, Blood 3 articles in 2022, Br. J. Dermatol. 2 in 2022, J. Immunother. Cancer 2021).

The team has also developed a strong and efficient valorisation policy, with 24 filed patents including 3 that supported the creation of 2 start-ups.

2) The team should be careful of the ratio between supervisors and bench work forces.

Nine PhD students have been trained in the reporting period, 7 having already defended their thesis. The number of PhD students recruited in 2021-2022 (2 including 1 Cifre thesis) is nevertheless low considering the number of HDR holders (8 at least). No national or international post-doctoral fellow has been recently recruited.

3) The team should think of refocusing its research on fewer projects.

Regarding the scientific strategy and projects, the interactions between the PIs in charge of the different research axes have increased. The number of subprojects has been reduced and research axes refocused: "CTCL group" and "melanoma group". These two groups have common research goals: identification of oncogenes/tumour antigens, immune escape mechanisms, strategies used by the tumour cell to escape antibody- or protein-inhibitor-based therapies. This has led to several co-authored publications. In addition, new national and international collaborations (such as one with the Dana Farber Cancer Center) have been established.

4) The development of the models of CTLC and melanoma should also be prioritized.

The team has generated a novel preclinical murine PDX model for CTCL (Cells, 2022).

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

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

Sous-total personnels non permanents en activité	**2**
Total personnels	**18**

EVALUATION

Overall assessment of the team

The overall assessment is excellent. The output of the team for clinical and translational research is excellent. The publication output in high-standard journals (e.g. Lancet Oncol., Blood, Br. J. Dermatol., J. Immunother. Cancer) is excellent. With 24 patents (3 being licensed to the industry) and the creation of two start-ups, the valorisation strategy is outstanding. The attractiveness is very good to excellent, with significant capacity for fundraising (PHRC, foundations, R&D contracts) and training activity (17 Master 2 and 9 PhD students, 7 having already defended their thesis with at least one first-author article). Only 2 PhD students have been recruited in 2020 and 2021 and are currently trained. The national and international recognition of the team is excellent.

Strengths and possibilities linked to the context

The team benefits from the complementary expertise of its members in basic research and clinical activities (long-lasting collaboration with the Dermatology, Pathology and Tumour Genomics departments of Saint-Louis Hospital). The access to large cohorts of patients' samples before and after treatment and to clinico-biological databases led the team to i) identify novel targets both on the tumour and immune sides and ii) better understand events leading to patients' resistance to ongoing therapies in both cutaneous T cell lymphoma (CTCL) and melanoma.

The team performs translational research with preclinical studies mainly on human samples, leading to several phase I/II clinical trials. Indeed, it has coordinated or is involved in several national and international trials (n=12 and 5, respectively).

The "CTCL group" identified several novel tumour markers (KIR3DL2, CD39/CD73 pathway, CD38, CCR8) for Sezary syndrome (Clin. Cancer Res. 2017, Blood 2022, Blood Adv. 2022, J. Invest. Dermatol. 2023). This led to the development of an anti-KIR3DL2 therapeutic antibody tested in a phase I/II clinical trial in Sezary syndrome. Some anti-tumour peptides have also been identified as new therapeutic agents for CTCL (J. Invest. Dermatol, 2021).

The "melanoma group" also identified several novel therapeutic targets in the tumour and investigated how cancer cells interact with the tumour microenvironment to promote tumour development and resistance to currently used treatments. In particular, the group developed a fast-processing tailored NGS panel of genes involved in molecular classification, prognosis and therapeutic resistance, coupled to a comprehensive analysis. This strategy allows to improve therapeutic management of melanoma. The group also promoted innovative multicentre phase I/II clinical trials (e.g. use of the tyrosine-kinase inhibitor nilotinib in unresectable Kit-mutated melanoma) and is involved in several international clinical trials (e.g. benefit of a combination therapy anti-PD1 + anti-BRAF/MEK inhibitor in metastatic melanoma, Nat. Med. 2020).

The team has published a considerable number of articles in the reporting period (more than 600). Although a large fraction of these publications originates from the clinical departments associated to the team, many are truly translational and involve work at the bench within the team.

The funding level of the team reaches approximately 400 k€ per year. It was awarded four PHRC grants, one INCA grant and twelve financial supports from dermatology societies, foundations or associations. Most of the team members are involved in European networks (EORTC, EAOD, EuroBloodNet).

The team has a strong valorisation policy with 24 patents during the period (with Inserm Transfert), mostly originating from their more basic research; three of them have been licensed to the industry for clinical use of therapeutic antibodies or anti-tumour peptides. This led to the creation of two start-ups (Aleraan Biotech and Jalon Thearpeutics). The team has also developed a strong and fruitful partnership (>1 M€) with industry or biotechnology companies (Innate Pharma, Alderaan Biotechnology).
Members of the team have a strong national and international recognition in the field of CTCL and melanoma. They are invited speakers to international conferences (>25) or are part of the organization committees of international scientific/medical events (e.g. AACR, EORTC, EAOD).

All PIs have reviewing or editorial activities (e.g. J. Invest. Dermatol., Blood, Nat. Commun.). They are also involved in the evaluation of grants and research programs and in teaching (Master 2, 'Diplôme d'études spécialisées').

The team is involved in general public activities and scientific dissemination (e.g. immersion of high school students in research labs, symposia for patients organized by patients' associations such as 'Ensemble Leucémie et Lymphomes Espoir').

Weaknesses and risks linked to the context

The number of PhD students currently trained is low (2 PhD students including 1 Cifre thesis) considering the number of HDR holders (8).

No post-doctoral fellow or visiting scientist has been hosted by the team during the period.

Generous funding has been obtained from national agencies and charities. Given the international recognition of the team members, seeking for international funds, in particular EU grants as PIs, is missing.

Although the team has refocused its research axes around common issues in CTCL and melanoma, the number of novel tumour targets of interest, particularly in CTCL, can be viewed as elevated.

Analysis of the team's trajectory

The trajectory of the team is a logical continuation of the research projects developed in the previous 5 years, taking advantage of well-annotated patients' cohorts and biosamples. While being sharply focused on the 2 skin cancers (CTCL and melanoma), the aims are nevertheless quite wide. They range from identification of prognostic and predictive biomarkers using hypothesis-free and hypothesis-driven approaches, to development and testing of therapies targeting the tumour cells/tumour microenvironment, and identification of immune mechanisms underlying tumour escape.

RECOMMENDATIONS TO THE TEAM

The team should prioritize publications as leading authors.

Given the international recognition of the team members, seeking for international funds, EU in particular, would be advisable.

It would be advisable for the team to focus on fewer biomarkers and promising targets in the CTCL field and, more specifically, focus on the targets where the team can be internationally competitive.

The team should make a deliberate effort to more actively attract young scientists, ranging from PhD students and post-doctoral fellows to new staff scientists well versed into omics approaches and bioinformatics analyses.

Team 2: Skin immunity and Inflammation

Name of the supervisor: M. Jean-David Bouaziz

THEMES OF THE TEAM

The team is composed of experts in immunology, inflammation and dermatology, who investigate the immunological mechanisms regulating inflammatory skin diseases. The research is carried out in close collaboration between dermatologists and plastic surgeons, allowing the team to span both fundamental aspects of research and translational approaches in clinics. The research program has been carried out along 5 main axes, which have been coordinated by 4 PIs and in particular: the role of regulatory T cells in inflammatory skin diseases; the role of interferons in interface dermatitis; the crosstalk between cutaneous and immune cells in healthy and inflammatory conditions; the role of stem cells in the modulation of inflammation and the immune regulation and treatment of inflammatory dermatosis.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous evaluation committee encouraged the PI to pursue in the same direction and to increase his international visibility. The team has increased their scientific production in terms of number of articles as well as their quality (Blood, PNAS, Nat. Commun., J. Invest. Dermatol.). The team leader is the president of the French society of dermatological research and the team organized the French congress of dermatological research twice (2017 and 2022) in the reporting period. The team was also awarded several International and European grants (e.g. Infinitus, Medimacs, Sanofi).

The committee also encouraged the implementation of regular lab meetings to foster intra-team exchanges. Accordingly, the team implemented team meetings and bibliography meetings in addition to weekly meetings that individual personnel hold with their respective supervisor. The team was encouraged to create synergy between the basic scientists and the various clinical departments (dermatology, plastic surgery, and internal medicine) associated with the team and these efforts have led to joint publications as well as patent applications.

Finally, the committee suggested the implementation of less targeted approaches to explore certain biological questions and the team has implemented several omics approaches in this direction.

Overall, the team has well addressed the recommendations of the precedent evaluation committee.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	6
Maitres de conférences et assimilés	1
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	4
Personnels d'appui à la recherche	6
Sous-total personnels permanents en activité	**17**
Enseignants-chercheurs et chercheurs non permanents et assimilés	1
Personnels d'appui non permanents	1
Post-doctorants	1
Doctorants	0
Sous-total personnels non permanents en activité	**3**
Total personnels	**20**

EVALUATION

Overall assessment of the team

The overall assessment is excellent. The scientific production of the team is very good to excellent with several notable contributions in Blood Adv., J. Invest. Dermatol., Nat. Commun. The team has an excellent attractiveness in terms of grants (4 ANR grants of which 2 as PI), collaborations at the national and international level (NIAID, NIH, USCF), and recognitions in the field. The PI is the president of the French Society of Dermatological Research and was the recipient of the 'grand prix' Robert Debré for research (2017). The contribution to society is excellent and resulted in 5 patents and in several International and European grants with industries (e.g. Infinitus, Medimacs, Sanofi).

Strengths and possibilities linked to the context

The team focuses on several aspects of inflammatory skin diseases from both fundamental and clinical perspectives. This focus in combination with the use of omics approaches (single cell sequencing, immune cells phenotyping etc.) allows to highlight similarities and differences that can be revealed for each of these specific diseases.

The team has produced 35 scientific publications in high-profile journals (including Blood Adv., J. Invest. Dermatol., Nat. Commun.) and more than 200 clinical ones that reflect the connections between fundamental, clinical and translational research activities of the team.

The team has obtained a significant number of grants from ANR (4 of which 2 as PI), in addition to contracts with industry (Brothier, L'Oréal, Calypso, Astra Zeneca, Médecine Innovation, Clarins, Sanofi, Capricor, Gallenic) on the development of new strategies to dampen skin inflammation and skin regeneration. Furthermore, it appears to have a good collaborative network (NIAID, NIH, and USCF).

The team research activities benefit not only from several technical platforms and animal facilities (Hospital Pitié-Salpêtrière-CyPS and Curie, ENS and Cochin multi-omics platforms) but also from the collaborations with the clinical departments (dermatology, plastic surgery, reference centre for rare diseases (MAGEC), and internal medicine) and from the access to clinical samples thanks to a collaboration with the 'Banque d'ADN et de Cellules, Genethon'. The team has been very successful in patenting (5 patents) and in translational research with participation in clinical trial studies. The team leader is recognized in his field of expertise (president of the French Society of Dermatological Research and recipient in 2017 of the 'grand prix' Robert Debré for research).

Weaknesses and risks linked to the context

The number of projects is large, opening up to the possible danger of dispersion of the resources of the team.

The current lack of post-docs is likely to be detrimental for the competitiveness of the team.

The team has published 35 research articles and over 200 clinical articles. However only half of the research articles bear members of the team in first or corresponding authorship position.

Analysis of the team's trajectory

The team gathers experts in immunology, inflammation and dermatology, who focus on several aspects of inflammatory skin diseases from both fundamental and clinical perspectives. The research program presented in the trajectory is composed of two main work packages: the characterization of the interplay between resident cutaneous cells, the immune system and the microbiota and the study of the immune-pathophysiology of recessive dystrophic epidermolysis bullosa and the characterization/exploitation of placental stem cell-based strategies to relieve this chronic inflammation. Each of these work packages addresses 4 and 3 specific aims, respectively. The specific goals set on the trajectory capitalize on the dual fundamental and clinical expertise of the team and are in line with their research activity in the past evaluation period. The project presented remains nonetheless large and particular attention should be paid to avoid dispersion along too many working aims.

RECOMMENDATIONS TO THE TEAM

Particular attention should be paid to avoid dispersion along too many working hypotheses.
The committee recommends to multiply efforts to recruit post-docs and young full-time researchers. This is critical to increase the dynamism of the team, prepare its renewal and strengthen the fundamental approaches currently carried out.

Team 3: Endothelium, Inflammation et Allogenicity

Name of the supervisor: Ms Nuala Mooney

THEME OF THE TEAM

The team's research activities are based on close collaboration between clinicians and basic researchers. The project focuses on investigating the mechanisms involved in graft rejection based on antibody-mediated rejection (ABMR). In particular, the team is investigating the role of endothelial cells in this process.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous evaluation committee recommended that the team increases collaborative projects with other teams in the unit and develops an active recruitment policy for PhD students, post-docs and young full-time researchers. In this context, Team 3 has established collaborative projects with Team 5 and Team 8. In terms of recruitment policy, although the number of PhD students supervised is very satisfactory (six defences during the reporting period), the recruitment of young full-time researchers remains an objective to be achieved.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	5
Maitres de conférences et assimilés	1
Directeurs de recherche et assimilés	2
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	3
Sous-total personnels permanents en activité	**12**
Enseignants-chercheurs et chercheurs non permanents et assimilés	3
Personnels d'appui non permanents	0
Post-doctorants	1
Doctorants	11
Sous-total personnels non permanents en activité	**15**
Total personnels	**27**

EVALUATION

Overall assessment of the team

The overall assessment is very good to excellent. The team's scientific output is very good to excellent, as shown by the large number of publications (284), including 33 basic-research publications in reputed journals in their field (e.g. Kidney Int., JCI Insight, J. Am. Soc. Nephrol.). Attractiveness is excellent. The team is recognized by the transplantation community, as evidenced with two major awards (TTS Outstanding achievement Transplantation science and CSL-Behring 'Prix de recherche') and the organisation of national and international conferences (e.g. SFHI annual meeting, ESOT conference and The Transplantation Society). The team was successful in raising grant funding (one PHRC and one FHU grants and four contracts with private companies). The team has very good to excellent public outreach activities, through its relations with industry and patients' associations.

Strengths and possibilities linked to the context

The team develops basic and translational research in organ transplantation, based on the strong link with Saint-Louis Hospital (one member of the team is also part of the Immunology department). It is organized in a quantitatively and qualitatively coherent way in term of permanent staff. Over the reporting period, the team trained eleven PhD students (whose 8 defended) and hosted one post-doc.

The work performed by the team has led to the characterization of mechanisms of the adaptive allogeneic immune response implicated in dysfunction of the solid organ allograft. Notably, the team identified B cell immune responses that underlie generation of pathogenic anti-HLA antibodies (DSA) and the appearance of graft ABMR. The pathways underlying the particular association between HLA-DQ directed DSA and loss of tolerance-promoting Treg differentiated by endothelial cells were unravelled. The team also showed the capacity of histone-mediated activation to alter endothelial-mediated responses.

Despite its relatively small size, the team produced a large number of publications (284 in the reporting period), including 33 original research articles (23 signed as first, last author or co-author), 11 reviews and 18 clinical articles related to the team's project, some of them in highly-reputed specialty journals (e.g. Kidney Int. 2019, JCI Insight 2021, J. Am. Soc. Nephrol. 2020, 2021). These publications are mostly first-authored by students in the team.

The team has been successful in raising funding as PI, including national grants from institutions (FHU, 100 k€; FEDER, 248 k€) and from funding agencies (PHRC, 380 k€; FRM, 100 k€). The team is also developing links with industry, as evidenced by funding from Jazz Pharmaceuticals, CSL Behring, Sandoz and Vitaeris, and the filing of one patent.

The team's recognition in the transplantation community is reflected in two major awards (TTS Outstanding achievement Transplantation science and CSL-Behring 'Prix de recherche') and the organisation of national and international conferences (e.g. SFHI annual meeting, ESOT conference and The Transplantation Society).

The team has developed strong links with clinicians, in particular through the participation in the organisation of the FHU-APOLLO (one member of the team is the coordinator). Two members of the team participate in the Sensitization in transplantation: Assessment of risk (STAR committees), created by the American Society of Transplantation.

Weaknesses and risks linked to the context

Although the team has obtained some funding during the reporting period, the lack of regular funding (i.e. no funding obtained in 2017, 2018 and 2021) puts the team's work at risk.

There was only one post-doc in the team over the reporting period.

Analysis of the team's trajectory

The team for the next contract will continue its research projects in transplantation and antibody-mediated rejection (ABMR) with the following aims:

- to better understand the function of HLA as a target of the humoral immune response in order to refine donor/recipient compatibility assessment pre-transplantation when organs are proposed to patients heavily sensitized against HLA and therefore have limited access to a compatible graft;

- to investigate the role of HLA molecules in peptide presentation, with the objective of comparing the allogenic potential of an HLA molecule for T with its allogenic potential for B lymphocytes;

- to pursue the characterization of T and B cell signatures allowing to predict differing phenotypes of rejection including disease severity and adverse outcomes notably by mapping the landscape of different adaptive immune cell types and to integrate these immunotypes into biological systems that will be linked to disease activity and severity.

The team composition will be reinforced by one DR Inserm who will be the new team leader and a CR Inserm. They will develop a project in link with their previous work, which was focused on the role of Pioneer Translation Peptides in immune tolerance and tumour cell rejection. They have made important contributions to their respective fields of research and the new larger team will offer an opportunity to deepen the collaboration on different aspects of immune tolerance by extending the application of their research to organ transplantation besides the current approach focusing on immune-based tumour therapies. The outcome of these studies aims at better understanding the role of MHC-I antigen presentation in organ transplant rejection.

RECOMMENDATIONS TO THE TEAM

An active policy of recruiting young researchers needs to be implemented.

The committee recommends to hire more students/post-docs and non-permanent staff to boost work at the bench.

The committee cautions the team against the development of too many projects.

The committee recommends to more focus the publications on the team's projects.

The committee recommends to reinforce collaborations with the other teams of Saint-Louis Research Institute, especially the ones also working in organ or hematopoietic cell transplantation. The structure of the new unit should be an asset to address this point.

In order to anticipate the arrival of the two new researchers, it is important to initiate scientific discussions with all members to define the scope of the future team.

Team 4: Immune responses in the immunocompromised host: Tolerance versus GVHD

Name of the supervisor: Ms Sophie Caillat-Zucman

THEMES OF THE TEAM

The team is involved in various projects at the interface between immunology, haematology and virology, aimed at deciphering the pathophysiological mechanisms of immune responses in the context of allogeneic haematopoietic stem cell transplantation (HSCT), but also in other situations such as HHV8-related diseases. The team is also working on new therapeutic approaches using CAR-MAIT cells to improve immune responses, in an allogeneic context, tumour recurrence after transplantation and viral infections in immunocompromised hosts.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous recommendations were the following:

The team should rapidly organize close interactions when their locations will be in the same building. The team should attract rapidly 1-2 full-time researchers for the success of the proposed project. Recruiting young scientists (at the PHD and post-doc level) must also be actively pursued. The committee strongly supports the excellent scientific project provided sufficient manpower is available to guarantee its feasibility.

This has been achieved since Team 4 has recruited a young full-time permanent researcher, 9 post-docs and 8 PhD students since the last evaluation.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	7
Maitres de conférences et assimilés	2
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	8
Sous-total personnels permanents en activité	**19**
Enseignants-chercheurs et chercheurs non permanents et assimilés	5
Personnels d'appui non permanents	0
Post-doctorants	9
Doctorants	10
Sous-total personnels non permanents en activité	**20**
Total personnels	**39**

EVALUATION

Overall assessment of the team

The overall assessment is outstanding. The team is led by two PIs with outstanding expertise in their field. The team has made outstanding scientific contributions to the field by publishing in high-profile journals (Sci. Immunol., Sci. Transl. Med., Nat. Med., Nat. Gen., NEJM, J. Clin. Oncol., Nat. Commun., Lancet Haematol., Cancer Discovery, J. Exp. Med., Blood). The team has an excellent to outstanding attractiveness with high fundraising capabilities (2 ANR grants, 2 INCa grants, 1 PHRC grant as PI) and training/mentoring activities. The team has made an outstanding contribution to society with its research activities in terms of industrial partnership and outreach activities (e.g. creation of the French Club of Young Immunologists, coordination of an open call 'Ambassadeurs de l'Immunologie').

Strengths and possibilities linked to the context

The team's achievements in the reporting period testify of strong interactions with clinical units and access to unique biological material. They uncovered critical insights into acute GVHD, microbiota-derived metabolites affecting regulatory T cells and surgical immune tolerance post-HSCT. They have also documented the reconstitution of the immunoregulatory landscape after HSCT. The team is actively involved in a translational project to understand the impact of azithromycin on relapse after allo-HSCT, resulting in a patent application. Importantly, they have addressed the potential use of MAIT cells in an allogeneic context and demonstrated their ability to delay the onset and severity of GVHD. They are working on the development of universal CAR-T cells based on MAIT cells for cancer therapy. The team has studied viral infections in immunocompromised hosts and developed an *ex vivo* model of bronchial mucosa. They are also investigating Castleman's disease caused by HHV8.

The team has published 58 original articles in high-profile international journals (e.g. Sci. Immunol., Sci. Transl. Med., Nat. Med., Nat. Gen., NEJM, J. Clin. Oncol., Nat. Commun., Lancet Haematol., Cancer Discovery, J. Exp. Med, Blood). In 20 of these publications, a team member is first and/or last author.

With the development of new omics tools, the team has focused on sharing raw data and source code to improve reproducibility and transparency in research. In line with this philosophy, they have published Guix, a new method for improving the reproducibility of computational environments in science with Guix (Nature Scientific Data 2022).

The team has demonstrated an outstanding fundraising capacity with more than 5 M€: 45 k€ from international calls (University of Pennsylvania, USA), 1 855 k€ from national academic programs as PI (2 ANR grants, 2 INCa grants, 1 PHRC grant, 'Direction Générale de l'armement, Cancéropôle Île-de-France'), 708 k€ from national investment programs (PIA « Grand défi Bioproduction », PIA « Maladies rares », Idex Université Paris Cité), 248 k€ from regional calls (DIM-TG Île-de-France) and 1 633 k€ from private partners (Alexion, Institut Carnot, Inserm Transfert) and 621 k€ from non-academic programs ('Fondation Maladies rares', 'France Leucemie Espoir', 'Association Laurette Fugain', 'Fondation pour la Recherche sur le Cancer'/SIGN'IT, 'Fondation pour la Recherche Médicale/Équipe FRM' 2022). The team had filled two patents during the reporting period.

The team's commitment to training and mentoring enables it to recruit PhD students and post-docs (plus 10 PhD students and 9 post-docs since the last evaluation).

Both leaders are internationally recognized and outstanding researchers in their field. They have been invited at numerous scientific conferences and one of the co-leaders was invited as a visiting professor at UCLA/ City of Hope in 2018. One of the co-leaders was Chair of the Board of the French Agency of Biomedicine from 2015 to 2021. Members of the team regularly participate in French research steering committees such as ANR, INCa, FRM and Fondation ARC. The recently recruited PI, together with four other colleagues, created the French Club of Young Immunologists (FCYI) under the auspices of the French Society of Immunology (SFI). He is now is a member of the board of the FCYI. The other PI is head of the scientific research pipeline of the National Reference Center for Castleman Disease. Five members of the team also participated in the "Day of Immunology 2021" by creating a presentation aid to visit elementary school and discuss with children about the immune system, microbes and vaccines. The team PI coordinated an open call ('Ambassadeurs de l'Immunologie') through the SFI to encourage researchers and clinicians to participate in this initiative. In addition, members of the team have participated in the 'Apprentis Chercheurs' initiative.

Members of the team received several prizes: 'Prix Victor et Erminia Mescle- FRM' (2019), 'Prix Brigitte MERAND jeunes chercheurs Force Hemato' (2022), 'Prix de Médecine de la Chancellerie des Universités' (2022), 'Prix de la recherche Laurette Fugain' (2022).

Weaknesses and risks linked to the context

There is no European funding.

Analysis of the team's trajectory

The merger of the two groups has had a positive impact on the team's translational goals. The scientific objectives are in line with the combined expertise of the two previous teams, and the projects show great complementarity for translational research in the field of immune response in immunocompromised hosts, with the important development of the CAR-MAIT approach. Both team co-leaders will reach retirement age in the next five years, but they have been wonderfully suited for the future takeover of the team by talented and dedicated young members.

RECOMMENDATIONS TO THE TEAM

The committee would recommend recruiting more academic researchers and post-docs and encourages researchers to apply for European grants to increase their visibility.

Team 5: Lymphocyte development and lymphoid disorders

Name of the supervisor: Mr Jean-Christophe Bories

THEMES OF THE TEAM

The team develops research projects aimed at i) better understanding early lymphopoiesis in humans, taking advantage of an elaborate xenograft model; ii) deciphering the role of a lncRNA, namely CRNDE, in the survival, tumorigenicity and drug sensitivity of multiple myeloma cells; iii) the development and preclinical testing of novel therapies against multiple myeloma, including bispecific T-cell engaging antibodies and double CAR-T cells. The team, composed of both researchers and physician-scientists with complementary expertise, develops translational research that has allowed generation of innovative treatments, on their way towards clinical testing.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Most of the recommendations in the previous report have been taken into consideration.

1) The team should pursue strong basic research to keep publishing in high-profile journals.

Members of the team have published basic research as first, last/corresponding author in high-profile journals (e.g. Immunity 2017, Leukemia 2021). In a large number of translational papers, team members appear as co-authors.

The team has also developed a strong valorisation policy, with 3 patents including 1 that has been licensed to Cytovia Therapeutics.

2) The team should maintain existing close interactions, and adopt a dynamic policy for recruitment of post-docs and students.

During the reporting period, the team recruited 7 post-docs and 6 PhD theses were defended attesting to the deliberate effort to train young scientists. In addition, one young scientist was hired as staff scientist by Inserm and joined the team.

3) The team should consider finding a partner in bioinformatics…

This has partially been covered through collaborations both within and outside IRSL. Moreover, a unit-wide effort is on-going to reinforce the local bioinformatics capacity.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	2
Maitres de conférences et assimilés	1
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	4
Sous-total personnels permanents en activité	**9**
Enseignants-chercheurs et chercheurs non permanents et assimilés	5
Personnels d'appui non permanents	0
Post-doctorants	4
Doctorants	7
Sous-total personnels non permanents en activité	**16**
Total personnels	**25**

EVALUATION

Overall assessment of the team

The overall assessment is excellent. The publication output is excellent in high-profile journals for basic research (Immunity, Cell Reports, PNAS), and translational/clinical research (Leukemia, Blood, Haematologica). The attractiveness is excellent with a high and diverse funding level (e.g. ANR, INCa, 'Fondation de France', ARC) and an important training activity (7 post-docs and 8 PhD students). The local and national recognition is excellent. The contribution to society is excellent in terms of valorisation (3 patents).

Strengths and possibilities linked to the context

The team benefits from the complementary expertise of its members in basic research in the field of lymphocyte development, and translational and clinical activities in the field of multiple myeloma pathophysiology and therapy. This middle-sized team is well structured gathering physician-scientists and basic researchers.

The group working on the dissection of early steps of lymphopoiesis *in vivo* using an interesting xenograft model, in which immunodeficient mice host neonatal human CD34+ HSC, is highly productive. An original and promising line of research relates to the role of lncRNA in growth and survival of multiple myeloma cells.

The development and preclinical testing of new therapies in multiple myeloma has led to promising patents, targeting in particular CD38. The close link of the team with the Saint-Louis Hospital clinical immuno-haematology department and with national networks ('Intergroupe Francophone du Myélome') is an asset for future clinical testing.

The team has published 73 articles during the reporting period, including 23 as lead authors in renowned fundamental journals, such as Immunity, Cell Reports, and PNAS, as well as in more translational journals, including Leukemia, Blood, Haematologica.

The funding level is high, reaching approximately 400 k€ per year from national calls, non-governmental programs and private partners (as PI with mainly 2 ANR grants for a total of 500 k€, 1 Inserm/Plan cancer for 179 k€ and an International Boston Medical Center Corporation for 94 k€, charities and private funds for a total exceeding 1.5 M€ (Laboratoires Servier, Cytovia Therapeutics Inc., « Intergroupe Francophone du Myélome », « Fondation de France » and' Fondation pour la Recherche sur le Cancer »).

The team trained several young scientists: six PhD theses defended and seven post-docs trained during the period.

The team is very well integrated within local and national haematology networks, in particular in the field of hematologic malignancies. Members of the team have a clear national recognition in the field of multiple myeloma and are part of many clinical and translational studies, as indicated by invitations in national (e.g. 'Société Française d'Hémalologie') and international (e.g. Symposium on CAR-T cell therapy) congresses.

Weaknesses and risks linked to the context

The highly productive group working on the early steps of lymphopoiesis is leaving the team.

The funding at the national and European levels is somewhat limited.

There is improvable international recognition.

Analysis of the team's trajectory

The size of the team will somewhat decrease with the departure of one PI. However, the ambitious project related to the evaluation, using high-throughput screens, of the contribution of lncRNAs in the proliferation, tumorigenicity and drug sensitivity of multiple myeloma cells should grow in the next 5-year period. The group working on next-generation therapies for multiple myeloma proposes translational projects using cell lines as well as patients' samples, as a logical follow-up of their previous work.

The team's future work is both ambitious given its clinical impact and feasible given the know-how of the team.

RECOMMENDATIONS TO THE TEAM

International recognition could be substantially increased through organization of international congresses, application to EU grants, and stronger involvement in international congresses and evaluation activities.
Pursuing a publication strategy of original papers (and authoritative review articles) in high-profile journals as lead authors would certainly further increase international recognition.

Given the strong international competition in the field of CAR-T cells, it might be wise to prioritize 'niche' and original projects over genome-wide screens aimed at identifying mechanisms of resistance to CAR-T cells.

Team 6: Pathophysiology of breast cancer

Name of the supervisor: Ms Jacqueline Lehmann-Che

THEMES OF THE TEAM

The team is dedicated to basic and translational research in the field of Breast Cancer (BC) with a particular focus on aggressive Triple Negative (TN) and Molecular Apocrine (MA) breast cancers subtypes. The objectives of the team are to define new biomarkers allowing to better characterize aggressive breast cancer subtype at diagnostic, to predict the response to treatment and propose specific treatment options. Another objective is to develop an innovative treatment strategy using optimized Extracellular Vesicles (EV) loaded with specific miRNA cocktail.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

As recommended by the previous committee, the team pursued its works in extracellular vesicle tool in order to develop an innovative strategy for the treatment of BC. The previous committee also recommended that the team hires more students/post-docs. Three PhD students have been recruited over the reporting period and two have defended their thesis but no post-doc was hired.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	3
Maitres de conférences et assimilés	4
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	3
Sous-total personnels permanents en activité	**12**
Enseignants-chercheurs et chercheurs non permanents et assimilés	1
Personnels d'appui non permanents	1
Post-doctorants	0
Doctorants	3
Sous-total personnels non permanents en activité	**5**
Total personnels	**17**

EVALUATION

Overall assessment of the team

The overall assessment is very good. The team's scientific output is very good with 56 original research articles including eight signed in first, last or corresponding author position in speciality journals (e.g. Front. Oncology, Cancers) and one in Nat. Commun. The team's attractiveness is very good. Team members are recognized as experts in the field of breast cancer and involved in different networks (e.g. EVOLVE France, Breast Centres network, GFCO). The team was successful in fundraising (e.g. 'Ligue Nationale Contre le Cancer', Canceropole IDF, GEFLUC). However, the number of PhD students and post-docs remains low. The contribution to society is very good with several outreach activities, including participation in events for the general public (e.g. 'l'arbre des connaissances', 'Octobre Rose'). It has industrial partnership and filled 2 patents.

Strengths and possibilities linked to the context

The team is organized in a quantitatively and qualitatively coherent way in term of permanent staff. Since 2019 (date of team creation), the team maintained a very good balance between scientific researchers and clinicians, and trained three PhD students and fourteen scientific and medical undergraduates.

The team has a multidisciplinary expertise combining the clinical and basic research in breast cancer based on the strong link with the 'Senopôle' (Saint-Louis Hospital) and also on the competences of team members in molecular and cellular biology, immunologic approaches and extracellular vesicle (EV) engineering. Notably, the team is highly involved in the identification of BC subtypes and the prediction of response. The team also identified a co-factor of NFAT3 with anti-tumoral and anti-metastatic capacities and used extracellular vesicles produced by NFAT3-expressing cells as therapeutic tools in aggressive breast cancer.

During the reporting period, the team has generated 61 publications: 56 original research articles and four reviews/commentaries and one Medecine/Sciences article and three book chapters. Eight of these original research articles were signed as first, last or corresponding author and published in reputed journals (Nat. Commun.) and most of them in speciality journals (e.g. Front. Oncology, Cancers).

The team has been successful in raising funds, including national grants from institutions (ITMO cancer (plan Cancer, 48 and 16 k€ as PI)) and Campus France (programme CEDRE, 8 k€ as PI)), from funding agencies ('Ligue Nationale Contre le Cancer' 300 and 60 k€ as PI) and also regional grants (Cancéropôle IDF, 27 k€ as PI), Region IDF (20 k€ as PI), GEFLUC (20 k€ as PI)). The team also has contracts with SATT and industries (SATT Erganeo, 58 k€ as PI, Novartis (2 x 20 k€ as PI) Sandoz (12 k€ as PI)). It has filled two patents related to the use of extracellular vesicles to treat breast cancer.

Several PIs of the team are recognized as experts in the field and are members of networks (EVOLVE France, DIM BioConvS, Breast Centres network, GFCO) or editorial board members of journals like Biomedicines, American Journal of Cancer Research. The team has strong interactions with national and international teams on breast cancer (BioSpectT, Godinot Institute, Reims, Bordeaux Institute of Oncology and IRCM, Montpellier, Bruxelles, Belgium and American University of Beyrouth, Lebanon). Members of the team are regular experts in steering committees such as HAS, INCa, ARC.

Team 6 is actively engaged in teaching and mentoring. They have demonstrated commitment to the education and training of students, providing guidance and supervision to the next generation of researchers through the involvement of team members in medical school and doctoral school of Université Paris Cité. Members of the team also coordinate specific teaching (DIU Maladies du sein) and annual congress on breast cancer ('Journées de sénologie de Saint-Louis') or cancer genomics (Journées GFCO).

The team is also involved in organising or participating in events for the general public, such as 'l'arbre des connaissances', 'action Déclics du cercle FSER' (meeting between high school students and researchers), 'Octobre Rose'.

Weaknesses and risks linked to the context

The ratio PhD students/HDR is low and no post-docs were trained in the team in the reporting period.

The European and international visibility of the team is low with few invitations in congresses and European network).

Although the team has obtained some funding during the reporting period, the lack of regular funding (no or low funding obtained in 2017, 2018 and 2019) puts the team's work at risk.

The number of publications signed as first, last or corresponding author is low.

Analysis of the team's trajectory

The team for the next term will continue its research projects on advanced and/or aggressive subgroups (triple negative breast cancer (TNBC), molecular apocrine breast cancer (MABC) and metastatic luminal breast cancer) with poor prognosis and treatment challenges, where new targets and new treatments are urgently needed. The team's project is declined in 3 complementary axes:

1/ deciphering the Molecular Apocrine Breast Cancers landscape in order to propose adapted therapeutics;

2/ development of original treatment strategies based on NFAT3 and extracellular vesicles;

3/ defining early predictive tools for BC response to treatments.

RECOMMENDATIONS TO THE TEAM

The committee recommends to hire more students/post-docs and non-permanent staff to boost the bench and also to recruit a scientific researcher to compensate the departure of one PI, which could contribute to increase the number of publications.

The team needs to increase its visibility. This can be done by participating in international congresses and by joining European networks.

The team is encouraged to apply for national and international funding.

Given the team's theme and scientific objectives, it could also develop more interactions with the private sector.

Given their strong research network at local/national level, there is the possibility to further enhance collaboration with other research teams, fostering new interdisciplinary projects and broadening the scope of their research, in particular with the other teams of Saint-Louis Research Institute. This last point should be facilitated by the structure of the new unit.

Team 7: Stem Cells Biotechnologies

Name of the supervisor: Mr Jérôme Larghero

THEMES OF THE TEAM

The aim of the team is to leverage cutting-edge materials and engineering processes to repair living tissues *in vivo* and to create living tissues *in vitro*. This involves the development of cell therapy and the use of scaffold and cell-printing paradigms, which offer scalable solutions for clinical applications.

Drawing on the team's expertise in stem cells, micropatterning, bioprinting, cell sheet technologies, and cell- and tissue-based applications, their primary objective is to integrate emerging engineering technologies with the goal of translating their research into clinical applications. There are three subgroups within the team, each focusing on three distinct themes: (i) *in utero* stem cell therapy: develop stem cell therapy as an adjuvant treatment in foetal myelomeningocele surgery to improve spinal cord repair and children's prognosis; (ii) tissue engineering: build tissues from cells and matrix; (iii) mesenchymal stem cells and autoimmune, inflammatory diseases: development of umbilical cord-derived mesenchymal stromal cells-based therapy.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Following the recommendations of the previous committee, Team 7 has made substantial efforts in the development of its policy with the recruitment of permanent positions as one associate professor at université Paris Cité, a full-time researcher by the Rothschild Foundation, one hospital practitioner, an engineer on a permanent contract and a future recruitment of one associated professor in 2025.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	3
Maitres de conférences et assimilés	1
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	6
Sous-total personnels permanents en activité	**10**
Enseignants-chercheurs et chercheurs non permanents et assimilés	6
Personnels d'appui non permanents	0
Post-doctorants	2
Doctorants	12
Sous-total personnels non permanents en activité	**20**
Total personnels	**30**

EVALUATION

Overall assessment of the team

The overall assessment is excellent to outstanding. The team's scientific output in translational and clinical research is excellent with 44 original research articles including 25 signed in first or last author position in speciality journals (e.g. Journal of the American College of Cardiology, Biomaterials). The team's attractiveness is excellent. It is internationally recognized in the field of stem cells and cell therapy with an important number of invitations to international meetings.

The team's commitment to education and mentorship is highlighted by the training of seven PhD students. The team was successful in raising grant funding (ANR, PHRC-N, FRM, iLite RHU).

The team has outstanding contribution to society, through its relations with industry including the transfer of their technologies and innovation by the creation of start-up (Astraveus industry) and seven patents. The team highlights their research to the public and the government by numerous actions including debates and hearing in the Senate and the National Assembly, conferences organized for patients' associations, reception of young high school students, and organization of thematic half-days for FRM and AFM donors.

Strengths and possibilities linked to the context

The team is at the forefront of a dynamic field that combines stem cell research with cutting-edge bioconstruction technologies. Its primary objective is to harness emerging engineering technologies and translate their research findings into clinical applications. Their projects hold substantial societal significance because they target various medical conditions, both in paediatric and adult populations, where existing medical solutions are lacking or insufficient.

The team has generated over the reporting period 44 publications including 25 articles directly related to their research theme (first and/or last authors) in the field of engineering technologies (e.g. Journal of the American College of Cardiology, Biomaterials, J. Tissue Eng. Regen. Med., Scientific Reports and Stem Cell Research Therapy).

The total budget is 850 k€ with diverse funding sources at the national level, in particular four ANR grants, including one in leading position, one PHRC-N grant, 'Agence de la Biomédicine', CEA, also one collaboration with iLite RHU. The team transfers their technologies and innovation by the creation of start-up led by their own staff as a PhD (Astraveus industry). Seven patents are associated to their activities including the invention of a microfluidic device with a flow-regulating chamber, and methods for generating cardiac progenitor cells for clinical use from primate embryonic stem cells, and their application.

Team members have actively participated in international and national congresses (e.g. American Association of pediatric otolaryngologist, '17e Soirée de la recherche Québecoise en ORL', International Network of esophageal atresia, Pediatric Dysphagia Serie, Aerodigestive Conference, Cincinnati Airway, 6th Conference of Confederation of European Otorhinolaryngology - Head and Neck Surgery, Course19th World Congress in Fetal Medicine, 'Club de Médecine Fœtale', 'Journées Neurosphinx', SFTCG, 'fondation ParisTech', LAAS Organ on a Chip Day, '33ème Journées Françaises de Cancérologie Digestive', Culture of cell spheroids in acoustic levitation and Conférence Acoustofluidics). All seniors have editorial responsibilities, and are regularly invited to conferences or scientific events organized by research actors, whether institutional or associative such as 'Congrès de la Société Française de Feotopathologie' and American Association of pediatric otolaryngologist. Several PIs of the team are recognized as experts in the field (winners of the MESCLE prize from FRM, the Emile Delannoy-Robbe prize from the Academy of Medicine). Four members of the team are part of the scientific councils of various learned societies and associations (e.g. 'Société Française de Pharmacie Oncologique', 'Comité Français de la Pharmacopée des produits biologiques et des Médicaments de Thérapie Innovante', 'Banque Française des Yeux and Inflamoeil'). The team leader is a member of the academies of medicine and pharmacy, the orientation council of the biomedicine agency, the research committee of FRM, vice-president of the biotherapies commission of the Medicen competitiveness cluster.

The team's commitment to education and mentorship is highlighted by training of seven PhD students, including 3 with the team leader (2 co-supervised outside the team), 4 with one PI of the team. The team leader was director of the HOB Doctoral School until 2020. As such, he actively cooperated with local and regional authorities, as well as several associations and/or foundations involved in PhD programs. He also participated to the creation of the EUR G.E.N.E ('École Universitaire de Recherche Génétique et Épigénétique Nouvelle École').

The team highlights their research by debates and hearing in the Senate and the National Assembly (bioethics law), training and education of professionals from Biomedicine Agency, conferences organized for patients' associations (e.g. Lions club evenings), reception of the public as part of the science festival, reception of young high school students in connection with the Tree of Knowledge association, organization of thematic half-days for FRM and AFM donors and ambassador of the communication campaign 'obstiné.es' of FRM.

Weaknesses and risks linked to the context

The team has a potential dependence on a limited number of funding sources. This can restrict their ability to sustain ongoing research and project expansion.

Limited availability of skilled researchers (CR), post-docs, and support staff (ITA) could hinder the team's ability to effectively manage and execute multiple research projects.
A limited number of permanent scientists manage PhD students.

The team may face risks related to data security, intellectual property protection, and potential breaches of confidentiality, especially when working with sensitive patient data and proprietary research findings.

Analysis of the team's trajectory

The team's trajectory shows a consistent growth in research activities over the years. They have expanded from an initial focus on a specific area to embracing multidisciplinary research. The team's research topics have evolved and diversified, reflecting an ability to adapt to emerging scientific challenges and trends. Their research trajectory indicates a positive shift towards more collaborative projects reflecting the team's openness to external collaborations.

The team has achieved significant publications, presentations at international conferences, and successful research projects. They have made noteworthy contributions to the advancement of knowledge in areas such as tissue engineering, with their work receiving recognition within the scientific community.

The team's trajectory showcases a commitment to scientific excellence and a positive impact on their field.

RECOMMENDATIONS TO THE TEAM

The committee recommends to hire more academic researchers and post-docs to boost the early career researcher position in a hospital environment.

The team should pay attention to the gender balance and the leadership of women in managing scientific projects.

Exploring a wider range of funding sources, such as grants from European (e.g. ERC) and international agencies, can provide additional resources for the team to pursue ambitious research projects.

The team should maintain and pursue its efforts to reinforce collaborations with Saint-Louis Research Institute.

Team 8: Physics of the cytoskeleton and morphogenesis

Name of the supervisor: Mr Manuel Théry

THEMES OF THE TEAM

The Cytomorpholab has two co-PIs physically located at two distinct sites: HIPI and the Institut de Recherche Interdisciplinaire de Grenoble (IRIG). The team's research is dedicated to the study of the mechanisms governing cell architecture and towards this aim, the team develops techniques, including microfluidic devises to uncover the physical laws that govern the generation of mechanical forces, migration, polarization, division and differentiation of cells. This expertise is applied to address several important questions to understand the mechanisms leading to stem cell differentiation on and how bone marrow environment impacts this development and differentiation (e.g. bone marrow on a chip).

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous evaluation committee recommended the team to hire additional personnel in the Grenoble campus in addition to reinforce the translational aspects of their research. Accordingly, the team has hired personnel thanks to the ERC consolidator of the first co-PI and the advanced one of the other one. The evaluation committee also recommended to strengthen the links with the hospital through recruitment of a scientist with a medical profile. The team has implemented the ties to clinics through a close collaboration with another HIPI team on the relationship between mechanical forces and stem cell functionalities and this collaboration has led to clinical trials in regenerative medicine.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maitres de conférences et assimilés	0
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	3
Sous-total personnels permanents en activité	**4**
Enseignants-chercheurs et chercheurs non permanents et assimilés	3
Personnels d'appui non permanents	0
Post-doctorants	1
Doctorants	8
Sous-total personnels non permanents en activité	**12**
Total personnels	**16**

EVALUATION

Overall assessment of the team

The overall assessment is outstanding. The team is led by two researchers with an outstanding expertise in the field of cell biology. Their contribution is well recognized in the elucidation of mechanisms controlling cell shape and polarity that impact their development and differentiation. The scientific production is outstanding with important contributions in high-profile journals (e.g. Nature Biomedical Engineering, EMBO, Current Biol., Nature Materials, and JCB). The attractiveness is outstanding as PIs have been recipient of three ERC grants (Starting and Consolidator for one co-PI and Advanced for the other co-PI). The contribution to society is excellent in light of the vulgarisation outreach.

Strengths and possibilities linked to the context

Over the reporting period, the multidisciplinary research performed by the team has provided important ground-breaking insights and generated new technical devices by developing a microfluidic circuit to create "a bone marrow on a chip", which opens the way to phenotypic diagnostics of leukemia and pharmaceutical screening. The results obtained by the team in stem cells through a collaboration with Team 7 provided the basis to address relevant pathophysiological questions in the clinics through clinical trials in regenerative medicine. They have been at the forefront of this field, initially working together to develop new tools to study the differentiation of hematopoietic stem cells (Nature Biomedical Engineering 2017). The team provided new insights into the importance of microtubule-generated forces in myeloid commitment of HSCs (EMBO Journal 2020) and documented new processes of stroma-mediated HSC polarization (The Journal of Cell Biology 2021), which could be of great importance for the treatment of some haematological malignancies.

The team produced 49 publications recognized in leading positions in high-profile journals (e.g. Nature Biomedical Engineering, EMBO Journal, Current Biology, Nature Materials, JCB).

The team raised more than 3 M€ from national and international calls (e.g. ERC Consolidator grant and 2 ANR grants) as well as non-academic programs (e.g. Fondation Bettencourt and Schlumberger).

The team is highly attractive with currently eight PhD students and 1 post-doc, reflecting its leading role in basic research.

Weaknesses and risks linked to the context

None identified.

Analysis of the team's trajectory

This team will not be part of the next contract, as such the trajectory was not assessable.

RECOMMENDATIONS TO THE TEAM

This team will not be part of the next contract, as such no recommendations were given.

Team 9: Human Systems Immunology & Inflammatory Networks

Name of the supervisor: Mr Vassili Soumelis and Mr Evanguelos Xylinas

THEMES OF THE TEAM

The team performs interdisciplinary research, using a combination of experimental and computational approaches to understand the complexity of the immune system exclusively in human physiology and diseases (oncoimmunology, inflammatory and infectious diseases). In particular, the team has been investigating cell state transition, multiple signal integration, adaptation to microenvironmental changes and cell-cell communication using immune cells, especially dendritic cells (DC) and T cells, as model. The team recently developed new research collaborative programs with local teams aiming to investigate the role of stromal cells in Castleman disease and the physiology of human secondary lymphoid organs and T cell diversity in diffuse large B cell lymphoma.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous committee alerted about the necessity to integrate the PI rapidly in the direction of HIPI, but this has not occurred.

The committee encouraged the team to hire a senior high-profile computational biologist with hard science basic training, which does not seem to have been achieved.

The committee suggested to have a strict management of the high number of projects through project interruption or reorientation if needed. The team has indeed stopped some projects but has also initiated new ones in coherence with the scientific and medical fields of Saint-Louis institution.

The committee encouraged the team to open their activities to translational research. Accordingly, the team initiated new research translational programs with several local teams, clinicians, and National Reference Centres of rare disorders with the objective to identify novel biomarkers or therapeutic strategies.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	1
Maitres de conférences et assimilés	1
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	3
Sous-total personnels permanents en activité	**7**
Enseignants-chercheurs et chercheurs non permanents et assimilés	1
Personnels d'appui non permanents	0
Post-doctorants	5
Doctorants	3
Sous-total personnels non permanents en activité	**9**
Total personnels	**16**

EVALUATION

Overall assessment of the team

The overall assessment is excellent to outstanding. The scientific production is outstanding with articles in top-tier journals (e.g. Nat. Cell Biol, Nat. Commun., J. Exp. Med., JACI, Cell, Science). The attractiveness is outstanding in terms of fundraising at the European and national levels (e.g. H2020 ImmunAID as PI, IMI IMMUcan as workpackage leader, 2 INCa grants, 8 ANR grants including 2 as PI, 2 FRM projects, 2 ARC foundation projects, PIA -Labex Inflamex and RHU COVIFERON as partner and PIA 'Maladies rares' as PI). The team has also welcomed eight post-doctoral fellows and eight PhD students and organized international scientific meetings. The contribution to society is excellent with five industrial partnerships in oncoimmunology.

Strengths and possibilities linked to the context

This interdisciplinary team, with an excellent gender balance, includes biologists, pharmacists, bioinformaticians, mathematicians, and clinicians with complementary expertise in biological and systems biology studies, with high commitment to translational research. The team integrates cutting edge technologies such as high-dimensional flow cytometry and transcriptomics, together with complex data analysis methods.

The team's achievements in the reporting period testify of strong interactions with clinical units and access to unique biological material, large cohorts of patients integrating biological and clinical information through European projects (IMMUcan project 628 k€ as partner and ImmunAID project 1 267 k€ as PI), and on-site platforms.

A main output was the development of a unique database of scRNAseq cancer studies from up to 3 000 patients (IMMUcan) that should provide a better understanding of the tumour microenvironment. Another main output is the development of a computational network to investigate cell-cell communication (ICELLNET) and the first mathematical models to study DC-Tcell communication. The team also contributed to the generation and management of unique patient-derived datasets (T-MEGA and MAARS) that are freely accessible resources to the community. These major scientific achievements could open broad perspectives for new classification, treatments, biomarkers, and diagnostic tools in a large variety of immune-related diseases (systemic autoinflammatory diseases, Covid, cancers, etc.).

During the reporting period, the team has published 47 original articles in high-profile journals (e.g. Cell, Science,), including 19 as last/corresponding author. Eight PhD students and eight post-docs were welcomed in the team and appeared as first authors in 20 of them.

The team has demonstrated a high fundraising capacity (>5 M€), from international calls (Mercatus Center US Fast grant COVID), European calls (H2020 ImmunAID as PI, IMI IMMUcan as leader of the Bioinformatics and Data Analysis workpackage), national academic programs (2 INCa grants, 8 ANR grants including 2 as PI) and non-academic programs (2 FRM projects, 2 ARC foundation projects), national investment programs (PIA -Labex Inflamex, PIA 'Maladies rares', 1 RHU).

The team has strong interactions with the non-academic world, as evidenced by Cifre contracts provided to PhD students by Sanofi and Servier and three industrial contracts for a total amount of 542 k€ with Sanofi, Elsalys (financed by BPI France). The team joined the Innovative Medicines Initiatives funded public-private partnership IMMUcan.

The team is internationally recognized in the field of dendritic cells and systems biology applied to immune responses in pathophysiology (organisation of international meetings, courses in system biology, summer schools). The team leader was granted the Lucien Tartois Prize from FRM in 2019 for excellence in immunology research not involving animal experimentation, as a significant recognition of his investment in human research.

Weaknesses and risks linked to the context

Despite a strong translational activity, the team has a limited participation in clinical trials and patent activity.

Computational biology plays an important role in the research programs of the team, however the team lacks a senior bioinformatician fully trained in theoretical aspects of the discipline.

The PI moved to Owkin - a full-stack AI biotech - in February 2022 and the team leadership was transferred to another PI (PU-PH, Bichat hospital) who has never published articles in collaboration with other members of the team. This change in leadership was not clearly communicated to team's members (e.g. PhD students/post-docs), and the new mentoring process was not properly organized as well, which has potentially destabilized the functioning of the team, especially regarding PhD students and post-docs.

The interdisciplinary dimension of the research topics (human immunology, infectious diseases, cancer, autoinflammatory disease, big data, and omics) poses the risk of dispersion of workforces.
The outreach activities are limited.

Analysis of the team's trajectory

This is not applicable as Team 9 will no longer be part of the next contract.

RECOMMENDATIONS TO THE TEAM

No recommendations were given as the team will no longer be part of the next contract.

Team 10: HLA-G immune checkpoint in Oncology and Transplantation

Name of the supervisor: Ms Nathalie Rouas-Freiss

THEMES OF THE TEAM

The team studies the role of HLA-G molecule in immune tolerance mechanisms in cancer and transplantation with the ultimate goal to translate this research into the clinic. The work includes the molecular characterization of HLA-G to use it as a biomarker or to inhibit its function by developing new experimental models.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

With regard to one of the main recommendations of the previous evaluation to *"continue to train young scientists in the future"*, eight doctoral theses are in progress and only four have been defended in the reporting period, two of which were co-supervised by external laboratories.

The previous report also recommended to focus the research project that was judged "*too broad*". The team outsourced certain parts of the project, such as the development of anti-HLA-G antibodies (using the pharmaceutical laboratories that developed the first anti-HLA-G therapeutic Abs) and the production of HLA-G proteins.

In addition, the report recommended "*a stronger focus on fundamental immunological mechanisms as well as the development of preclinical models*". A greater emphasis on fundamental immunological mechanisms was achieved through the identification and characterization of a new sub-population of T lymphocytes expressing ILT2+ that could provide an insight into the mechanisms of tolerance induced by HLA-G. Finally, the team developed a tumoroid methodology as a new preclinical model.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	5
Maitres de conférences et assimilés	2
Directeurs de recherche et assimilés	5
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	6
Sous-total personnels permanents en activité	**19**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	7
Post-doctorants	0
Doctorants	8
Sous-total personnels non permanents en activité	**15**
Total personnels	**34**

EVALUATION

Overall assessment of the team

The overall assessment is very good to excellent. The scientific production in basic, translational, and clinical research is very good with articles published in e.g. Cancer Immunol. Res., J. Heart Lung Transplant., Hum. Immunol., Cancer Lett., Front. Immunol., Front. Oncol. The attractiveness is very good to excellent with a strong recognition of the team in the field, its fundraising capacities and the training of eight PhD students. The contribution to society is outstanding in light of patenting activities (4 patents) and industrial partnerships, including one Cifre contract and very active dissemination strategy to the general public.

Strengths and possibilities linked to the context

The team is leader in the study of tolerance induced by the HLA-G molecule.

The discovery of immune checkpoints and the clinical success of immune checkpoint inhibitors have allowed to reconsider HLA-G as an immune checkpoint. This is undoubtedly a strength for the field of HLA-G research.

The interactions with clinicians are strong, including participation in numerous clinical trials in oncology. This collaboration has been productive with several publications (28 peer-reviewed papers) in specialized journals e.g. Cancer Immunol. Res., J. Heart Lung Transplant., Hum. Immunol., Cancer Lett., Front. Immunol., Front. Oncology.

The team coordinates an INCa PRTK2018 grant (530 k€) and was partner in an ANR grant (800 k€).

The team's work in the field is unrivalled, as demonstrated by i) the organization of international conferences and workshops every three years, ii) regular invitations to national and international conferences for oral presentations, iii) the participation to the boards of numerous learned societies (e.g. 'Société française de Radiothérapie Oncologie', 'Agence de Biomédecine', European Section of Urological Research, 'Commission de recherche Clinique') and to institutional committees and juries (Hcéres, thesis, HDR…), iv) editorial responsibilities. Team members also received two awards ('trophée de l'APHP' and 'prix Jean Bernard').

The team trained 8 PhD students during the reporting period.

The team has a strong interest in innovation and transfer to industry, as marked by th-e filing of four patents during the reporting period, the establishment of contracts/partnerships with private companies (ArgenX, Roche, and Mylan) and the collaboration with Invectys through a Cifre grant for a PhD student. They also provide expertise and recommendation to national bodies and public administrations (including CEPH, 'Agence de Biomédecine', 'Association Oncodéfi', 'commission des plis cachetés de l'Académie des Sciences'). The team is associated with the European Consortium REBORNE (7th PCRD).

Members of the team are very active in public outreach and dissemination to social, economic, and cultural actors, including numerous participations to main media (e.g. Le Figaro, Paris-Match, Europe 1, RFI, France Inter), or production of didactic films and videos.

Weaknesses and risks linked to the context

Many funds will end shortly after the evaluation period. Note that new grants have been obtained from ANR, PEPR, INCA, FRM, and Vaincre la mucoviscidose, for a total amount of 1,700 k€ for the team, which will provide funding for the next four years.

High-profile publications in leadership positions are limited.

Although the work on ILT2+ T cells is very promising, the team's translational approach is not sufficiently supported by fundamental research, in particular to understand the molecular mechanisms of HLA-G-induced immunomodulation.

Analysis of the team's trajectory

The future team will consist of the same number of researchers, thanks to the replacement of two retirements by two recruitments via CEA. The projects are in part already funded and in part under evaluation.

The scientific projects will be the follow-up of the two present axes, namely the study of HLA-G in oncology, and the clinical importance of HLA-G in allogeneic transplantation.

The study of the role of HLA-G in oncology will focus on the further characterisation of the ILT2+ T lymphocyte subpopulation identified by the team, combining basic research with a more translational approach in the context of metastatic tumours (kidney and bladder). The team is also planning to develop a new project based on internal results and the results of a clinical trial showing the value of targeting ILT4, one of the HLA-G receptors, on the surface of the tumour cell. With regard to HLA-G in the context of transplantation, the team will pursue two objectives: (i) to characterise HLA-G as a predictive marker of lung allograft rejection, (ii) to exploit the graft tolerizing function of HLA-G to improve the efficacy of skin grafts in different settings.

RECOMMENDATIONS TO THE TEAM

The committee recommends hiring young scientists to rejuvenate the team as well as post-doctoral fellows.

The committee recommends to target higher-quality journals for future publications.

The committee recommends that the team continues to develop basic research in parallel to clinical research, particularly to understand the molecular mechanisms underlying the immunomodulatory activity of HLA-G.

Exploring a wider range of funding sources, such as grants from European agencies (e.g. ERC), could provide additional resources for the team to pursue its ambitious research projects.

CONDUCT OF THE INTERVIEWS

Dates

Start: 14 December 2023 at 08:00

End: 15 December 2023 at 18:00

Interview conducted: **on-site**

INTERVIEW SCHEDULE

Day 1 of the interview 14/12/2023

8:00-8:25	**Hcéres committee meeting** *Closed-door meeting*
8:25-8:30	**Hcéres rules and procedures *by M. Mercier-Bonin*** *Public session (all unit members)*
8:30-9:20	**Scientific and administrative presentation of the unit** 30 min presentation (including unit's trajectory) + 20 min discussion *JC. Bories* *Public session (all unit members)*
9:20-9:40	**Coffee break**
(9:40-12:30)	**Scientific presentations by team leaders 1/2** 20 min presentation (including team's trajectory) + 10 min discussion *Public session (all unit members)*
9:40-10:10	**Team 1**
10:15-10:45	**Team 2**
10:50-11:20	**Team 3**
11:25-11:55	**Team 4**
12:00-12:30	**Team 5**
12:30-13:30	**Lunch break & committee debriefing** *Closed-door meeting*
(13:30-16:40)	**Scientific presentations by team leaders 2/2** 20 min presentation (including team's trajectory) + 10 min discussion *(note: for Teams 8 & 9, no trajectory presentation so 15 min presentation + 10 min discussion; for Team 11, 15 min presentation (including team's trajectory) + 10 min discussion)* *Public session (all unit members)*
13:30-14:00	**Team 6**
14:05-14:35	**Team 7**
14:40-15:05	**Team 8**

15:10-15:35	**Team 9**
15:40-16:10	**Team 10**
16:15-16:40	**Team 11 (Atip-Avenir, *not evaluated*)**
16:40-17:00	**Coffee break & committee debriefing** *Closed-door meeting*

Committee splitting in three sub-groups for collective meetings with staff

17:00-17:40	**Meeting with ITAs (in French)** *In the absence of any managing staff (director, team leaders)*
17:00-17:40	**Meeting with researchers** *In the absence of any managing staff (director, team leaders)*
17:00-17:40	**Meeting with post-docs and students** *In the absence of any managing staff (director, team leaders)*
17:40-18:15	**Committee debriefing** *Closed-door meeting*
18:15	**End of the first day**

Day 2 of the interview 15/12/2023

8:30-9:00	**Committee debriefing** *Closed-door meeting*
9:00-09:50	**Meeting with institution representatives: Université Paris Cité & Inserm** *Closed-door meeting*
9:50-10:10	**Committee debriefing** *Closed-door meeting*
10:10-11:00	**Meeting with the Director of the unit** *Closed-door meeting*
11:00-12:00	**Committee debriefing & Redaction of the final report 1/2** *Closed-door meeting*
12:00-13:00	**Lunch break**
13:00-16:00	**Redaction of the final report 2/2** *Closed-door meeting*
16:00	**End of the interview**

GENERAL OBSERVATIONS OF THE SUPERVISORS

Université Paris Cité

Le Président

Paris, le 6 février 2024

HCERES
2 rue Albert Einstein
75013 Paris

Objet : Rapport d'évaluation de l'unité **DER-PUR250024171 - HIPI - Immunologie humaine, pathophysiologie et immunothérapies.**

Madame, Monsieur

L'Université Paris Cité (UPCité) a pris connaissance du rapport d'évaluation de l'Unité de Recherche **HIPI - Immunologie humaine, pathophysiologie et immunothérapies.**

Ce rapport a été lu avec attention par la direction de l'unité, de la part de laquelle vous trouverez deux courriers ci-joint, 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.

Présidence

Référence
Pr/DGDRIVE/2023

Affaire suivie par
Christine Debydeal - DGDRIVE

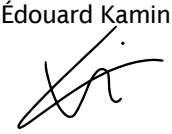
Adresse
85 boulevard St-Germain
75006 - Paris

www.u-paris.fr

Je souhaite souligner, avec le Doyen de la Faculté de Santé, que l'HIPI est une UMR d'excellence dans sa thématique. Dans le cadre de la structuration de la recherche au sein de la Faculté de Santé d'UPCité, cette UMR sera un des éléments constituants du futur centre de recherche IRSL. La création de ce centre de recherche a été accompagnée par les tutelles après avis d'un scientific advisory board, et a conduit à de profondes restructurations des équipes constituantes. Ce centre de recherche augmentera la lisibilité, la visibilité et le rayonnement de la recherche sur le site de Saint Louis en particulier, et de façon plus générale au sein de l'université.

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

Édouard Kaminski



HIPI
Human Immunology
Pathophysiology
Immunotherapy

Inserm | Université de Paris

Unité mixte de recherche Inserm 976

Directeur :
Jean-Christophe Bories

Paris, le 24/01/2024

Madame, Monsieur,

Veuillez trouver ci-joints nos observations générales concernant le rapport HCERES de l'évaluation de notre unité de recherche (UMR_S976, HIPI).

Observations:
We have read the report from the HCERES committee and thank experts for the quality of their work and for the constructive discussions during the auditions. We are pleased to note that the committee concluded that the global performance of HIPI was excellent. Furthermore, the trajectory and the proposed scientific program was considered as having strong potentials for clinical applications, as well as for education and training.

More specifically, the integration of HIPI research activities in the society was considered as outstanding, and the scientific production and the attractiveness both excellent. While our scientific objectives and resources were judged outstanding/excellent, concerns were raised about some aspects of the functioning of the unit.

We agree on this very last point and we would like to stress, as acknowledged by the experts (and as we did many times during the last years), that the old premises and the scattered localization of the labs on the hospital area had a very negative impact on the working conditions and did not favour internal communication. Moreover, despite the attractiveness of our research, this situation has made it difficult the durable settlement of top scientists in the unit, and, while one team has been recruited, another has left.

We believe that the decision to merge all the existing research units from the site of Saint-Louis into a new UMR will help to improve these issues. However, only a strong commitment of the supervising bodies in modernizing and renovating the premises could ameliorate the working conditions and eventually make the research centre even more competitive.

Jean-Christophe Bories

The Hcéres' evaluation reports are available online:
www.hceres.fr

Evaluation of Universities and Schools
Evaluation of research units
Evaluation of the academic formations
Evaluation of the national research organisms
Evaluation and International accreditation

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