Research evaluation

EVALUATION REPORT OF THE UNIT

EMiLy - Écotaxie, Microenvironnement et développement lymphocytaire

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

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High Council for evaluation of research and hignter education

In the name of the expert committee :

Matteo Iannacone, chairman 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

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Experts:	Mr Gilles Blancho, CHU de Nantes (representative of CNU) Mr Stefano Casola, IFOM ETS - The FIRC Institute of Molecular Oncology, Italy Ms Mireia Pelegrin, CNRS, Montpellier (representative of CSS Inserm) Ms Clara Maria Scarlata, Centre de Recherche en Cancérologie de Toulouse (supporting personnel)

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Mr Pierre-Emmanuel Rautou, UFR de médecine - Université Paris Cité
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Mr Philippe Ruszniewski, UFR de médecine - Université Paris Cité
Ms Sabine Sarnacki, UFR de médecine - Université Paris Cité
Mr Benjamin Terrier, Inserm
Mr Michel Vidal, Faculté de Santé - Université Paris Cité

CHARACTERISATION OF THE UNIT

- Name: Écotaxie, Microenvironnement et développement lymphocytaire
- Acronym: EMiLy
- Label and number: U1160
- Composition of the executive team: Mr Antoine Toubert (director) and Mr Karl Balabanian (deputy director)

SCIENTIFIC PANELS OF THE UNIT

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

THEMES OF THE UNIT

The research unit is dedicated to explore a wide array of topics within immunology and haematology, seamlessly integrating various themes into a cohesive study. Central to their focus is the examination of microenvironmental niches and their impact on immune regulation. This involves investigating how specific organ niches, such as those in the bone marrow, thymus, and gut, influence the behaviour and regulation of immune lymphoid cells, especially under conditions like cancer.

A significant portion of their research is devoted to understand the dynamics of hematopoietic stem and progenitor cells (HSPCs). This involves studying their development and differentiation in bone marrow niches and assessing their critical role in maintaining the balance of the blood system. The unit delves deeply into the cellular and molecular mechanisms that govern the function of these essential cells.

Interactions within immune niches form another key area of their studies. Here, they explore the complex interplay among various cell types, including endothelial cells and mesenchymal stem/stromal cells, focusing on how these interactions affect immune cell differentiation and function. Special attention is given to B cell progenitors and plasma cells.

The unit also addresses immune responses in various pathological conditions, such as different types of cancers and immunodeficiency. They are particularly interested in conditions like WHIM Syndrome and MyeloDysplastic Syndromes. Their approach involves utilizing advanced methodologies like 3D culture assays, omics technologies, and mouse models. Moreover, they maintain strong collaborative ties with clinicians and international partners, fostering translational research.

Their studies extend to a detailed examination of diverse immune cells like HSPCs, plasma cells, and natural killer cells, investigating their roles in both health and disease. The unit also places a strong focus on thymic function and T-cell repertoire, especially in the context of human immunology related to aging and regeneration of thymic functions.

Furthermore, they investigate the role of immune cells in gastrointestinal and skin diseases, such as inflammatory bowel diseases and colorectal cancer. The unit's commitment to clinical implications and translational research is evident in their work on post-operative recurrence in Crohn's disease, immune reconstitution in various clinical settings, and the identification of new therapeutic targets in colorectal cancer.

In summary, the unit's approach is comprehensive, integrating cutting-edge research in immune niches, cell-cell interactions, and the roles of immune cells in various diseases, thereby contributing significantly to the field of immunology and haematology.

HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

The Inserm U1160 research unit, titled "Microenvironment, Lymphocyte Development and Homing," EMiLy has a rich history and a strategic geographical location. It was initially part of the "Alloimmunity-Autoimmunity-Transplantation" (A2T) unit during the 2014-2019 period. This period saw the unit focused on lymphocyte differentiation and homeostasis in allo- and autoimmunity, regulation of allogeneic immune responses in renal transplantation, and hematopoietic stem cell transplantation. In 2019, Inserm U1160 underwent significant restructuring. It integrated three permanent researchers from Inserm U996 and U1197. This move marked a shift towards a more focused research agenda. In the current structure (post-2019), the unit comprises three main teams. Team 1 focuses on homeostatic and pathological chemokine-regulated interplays between lymphocytes and their microenvironment. Team 2 is dedicated to thymic function and development, incorporating research on iNKT development and thymic function in human health and disease. Team 3 concentrates on Intestinal immunity in inflammation and cancer, combining expertise in inflammatory mucosal immunity and oncoimmunology.

The unit includes a medium-sized team of around 50 members, with a diverse composition of permanent researchers from Inserm and Université Paris Cité-APHP, hospital practitioners, technicians, engineers, and administrative support staff. The integration of external researchers and the collaboration with hospital professionals highlight the unit's commitment to translational research and clinical applications.

All teams are housed in the Institut de Recherche Saint-Louis (IRSL), located at the Saint-Louis Hospital campus of Université Paris Cité (UPC). The unit benefits from shared facilities including technological and methodological platforms for flow-cytometry, cell sorting, genomics, gene-expression arrays, bioinformatics, and an animal facility. These activities are structured within UMS/UAR Saint-Louis.

In summary, Inserm U1160 has evolved into a focused, collaborative, and well-equipped research unit, strategically located at IRSL in Saint-Louis Hospital, with a strong emphasis on lymphocyte development, chemokine-regulated interactions, thymic function, and intestinal immunity in inflammation and cancer.

RESEARCH ENVIRONMENT OF THE UNIT

The unit primarily engages in basic research with significant translational aims, integrating seamlessly with other research units in Haematology, Oncology, and Immunology. There is a close collaboration with clinical departments of Saint-Louis Hospital, particularly in Haematology and Dermatology. This is exemplified by Team 3 (led by a PU-PH in Gastroenterology), which bridges basic, translational, and clinical sciences.

The current director of EMiLy also presides over the IRSL scientific board and directs the Inserm/CNRS/UPC US53/UAR2030 "Saint-Louis", created in 2021. Team leaders and members actively participate in campus management, contributing to the IRSL scientific board, University Paris Cité, and the École Doctorale "HOB" committees. They are also deeply involved in teaching activities and PhD supervisions, underscoring a commitment to academic development.

The unit is a partner in several 'Plans d'Investissement d'Avenir' (PIA) programs, which include IHU2 2018 THEMA, Institut Carnot 2020 OPALE, FHU Prosthetic Joint Infections (PROTHEE), FHU Innovative Therapy for Immune Disorders (TRUE), SIRIC inSiTu Integrated cancer research site, and Labex 'Milieu intérieur' and LERMIT. These partnerships involve steering committee roles and collaborations with other leading research and clinical institutions, enhancing the unit's capabilities and impact.

The unit is a member of the Cancéropôle Ile-de-France and a founding board member of the 'Instituts Hors Murs' 'Immunologie et Immunopathologie' and 'Maladies ostéoarticulaires' of Université Paris Cité.

The unit has active collaborations with clinical cooperating groups, including the 'Groupe Francophone des Myélodysplasies' (GFM) and the 'Groupe Français d'Etude des Lymphomes T cutanés' (GFELC). These collaborations foster a robust continuum between research laboratories and care structures, crucial for translational research.

In summary, the research environment of EMiLy is a dynamic and collaborative ecosystem, with strong links between basic research and clinical application, supported by participation in significant national programs and regional clusters, and led by a team actively involved in both research and academic governance.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	6
Maîtres de conférences et assimilés	1
Directeurs de recherche et assimilés	3
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	7
Sous-total personnels permanents en activité	**19**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	4
Post-doctorants	2
Doctorants	11
Sous-total personnels non permanents en activité	**17**
Total personnels	**36**

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	7	0	2
Inserm	0	5	5
Autres	4 (APHP)	0	0
Total personnels	**11**	**5**	**7**

GLOBAL ASSESSMENT

The 'Écotaxie, Microenvironnement et développement lymphocytaire' (EMiLy) research unit, under the supervision of Université Paris Cité and Inserm, has been evaluated as excellent. The unit boasts a comprehensive approach, integrating immunology and haematology, with a particular emphasis on understanding microenvironmental influences on immune regulation and hematopoietic stem cell dynamics. Their dedication to explore the interaction of immune cells with their niches, particularly in the bone marrow, thymus, and gut, is commendable and aligns with their thematic focus on immunity, infection, and immunotherapy.

The unit has made significant strides in providing novel mechanistic insights into CXCR4 signalling. Their groundbreaking studies have elucidated the regulation of lymphoid potential of hematopoietic stem and progenitor cells, osteogenic fate of bone marrow stromal cells, and plasma cell homing, differentiation, and function. This research is not only foundational but also paves the way for potential therapeutic innovations.

In addition, EMiLy's research on the genetics of thymic function is pioneering, offering a clearer understanding of thymopoiesis in healthy adults. Their robust study involving a large cohort of individuals has defined genetic controls of human thymopoiesis, marking a substantial contribution to the field and potential implications for aging and immune system regeneration.

EMiLy's unit represents a robust integration of basic, translational, and clinical sciences, making strides in immune regulation and disease understanding through a collaborative and translational approach. The unit has developed strong connections with clinical departments and international partners, fostering a rich environment for innovative research. This is particularly evident in their strategic involvement in significant national programs like IHU2 THEMA and Institut Carnot OPALE, as well as regional clusters which have boosted their research capabilities and outreach.

The unit's dynamic research environment is a testament to its commitment to bridging basic research with clinical applications. Their participation in high-value collaborative programs and initiatives, coupled with an active role in both research and academic governance, marks EMiLy's significant position in the scientific community. The team leaders and members have been invited to share their insights and findings at prestigious international conferences, such as the Gordon Research Conference and the European Congress of Immunology, further emphasizing their international standing.

EMiLy's scientific production is not just prolific but also impactful, marked by high-quality publications in leading journals with a general audience (J. Exp. Med., PNAS, Sci. Transl. Med., Nat. Commun.) and top-level specialty journals (Blood, Leukemia, Gut, Br. J. Dermatol., J. Immunol., Cancer Immunol. Res., J. Immunon. Ther. Cancer). This work has led to innovative contributions to the field of immune regulation and disease. The unit has been successful in securing numerous grants as principal investigators from various respected sources, including national agencies like ANR and INCa, and international collaborations. Specifically, the unit has managed to secure a substantial budget, with a recurrent budget of 210 k€ per year supplemented by external funding sources, which constitutes approximately 2/3 of the total budget. This financial capability has enabled them to pursue ambitious projects and maintain state-of-the-art facilities.

The unit's commitment to societal impact is clear from its active engagement with patients' associations and formation of industrial partnerships. They have established about ten industrial contracts and collaborations with entities like X4 Pharmaceuticals and Sanofi-Aventis, and have registered a total of six patents, including methods to obtain lymphoid progenitors and innovative CXCR4 antagonists. Their commitment to societal outreach is further demonstrated through initiatives aimed at the general public, including open-door meetings with patients and the program 'l'arbre des connaissances – apprentis chercheurs'.

In terms of human resources, the unit has nurtured a thriving environment with PhD students and post-doctoral fellows contributing to the research endeavors. The gender balance and psycho-social risks are vigilantly monitored, ensuring a conducive and equitable working environment.

In summary, the EMiLy research unit exemplifies excellence in scientific research, with notable contributions to understanding immune niches, cell-cell interactions, and the roles of immune cells in health and disease. Their innovative approaches, collaborative spirit, and dedication to translational research make them a valuable asset to the scientific community and society at large.

DETAILED EVALUATION OF THE UNIT

A - CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

The unit has taken various actions in response to the recommendations from the previous evaluation report. Below is a summary of these actions, categorized according to the key areas of recommendation:

1) Scientific production and activities

- *Pursuit of high-profile publications:* it has been successfully implemented across all teams, focusing on quality over quantity and utilizing clinical cohorts more effectively.

2) Unit's organization and life

- *Gender equity*: actions taken include (i) promoting women to leadership roles; (ii) supporting women's applications for grants (e.g. ERC consolidator grant) and leadership positions in scientific organizations; (iii) ensuring gender parity in visiting speakers and other initiatives; (iv) addressing the disparity in senior management gender balance.

- *Technician placement clarity*: despite challenges, the unit has managed to address technician placement issues by hiring non-permanent staff funded through external grants.

- *Inclusive meetings*: quarterly board meetings now involve all research staff.

- *Distribution of technical staff*: while facing limitations in recruiting permanent technical staff, the unit prioritized new recruitments to understaffed teams.

3) Scientific strategy and projects

- *Clinical cohorts*: the strategy has been adjusted to ensure added scientific value is primarily generated within the unit.

- *Technology and expertise development*: single-cell sequencing facilities and bioinformatics support have been addressed by on-site technology, training of PIs and staff, recruitment of PhD students with bioinformatics training, and outsourcing where necessary. A dedicated technician for humanized mouse models is a current priority, with discussions ongoing with funding agencies.

4) Future planning

- *Leadership transition*: the unit has been proactive in planning for future leadership, with a deputy director appointment in 2020 to oversee the evolution of the unit for the next contract.

In summary, EMiLy has actively addressed the recommendations from the previous evaluation, focusing on enhancing scientific output, improving organizational structure and gender equity, and strengthening their scientific strategy and technological capabilities. The unit has also taken steps to ensure smooth leadership transition in the future.

B - EVALUATION AREAS

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

Assessment on the scientific objectives of the unit

The scientific objectives, which are in line with the merge between the 'Institut Universitaire d'Hématologie' (IUH) and the 'UFR de Médecine' of the 'Faculté de Santé' (Université Paris Cité), are excellent. The unit has an excellent research development, integrating a wide array of topics within immunology and haematology, into a cohesive study. The collaborative ties with clinicians foster strong translational research.

Assessment on the unit's resources

The unit's resources are excellent. It has an excellent capacity to acquire additional financial resources, at national and international levels, over and above its recurrent budget. The seamless integration between basic scientists and clinicians is commendable.

Assessment on the functioning of the unit

The functioning of the unit is excellent. There is an excellent organization of the work spaces; each team has a dedicated space for cell culture and specific experiments, the rest of the space is shared by all the teams. The gender balance is excellent, except for PI positions. The unit is vigilant about psycho-social risks in laboratory practice. There is an excellent monitoring of data protection ensured by the application of recommendations from Inserm as well as by the use of electronic laboratory notebooks. The unit has an excellent capacity to manage emergency situations (e.g. Covid-19 pandemic crisis).

1/ The unit has set itself relevant scientific objectives.

Strengths and possibilities linked to the context

The unit explores a wide array of topics within immunology and haematology, which are seamlessly integrated into a cohesive study. Central to their focus is the examination of microenvironmental niches and their impact on immune regulation. This involves investigating how specific organ niches, such as those in the bone marrow, thymus, and gut, influence the behaviour and regulation of immune lymphoid cells, especially under conditions like cancer.

The unit achieves these scientific objectives and missions in line with the merge between the 'Institut Universitaire d'Hématologie' (IUH) and the 'UFR de Médecine' of the 'Faculté de Santé' (Université Paris Cité). This environment allows basic research with a translational aim. The different teams of the unit developed collaborations with clinical departments of Saint-Louis Hospital in Haematology, Dermatology, Gastroenterology, Infectious diseases. The unit fosters research development in the field of leukemia through the partnership and board participation in the PIA IHU THEMA and in the Institut Carnot OPALE.

Weaknesses and risks linked to the context

None identified.

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

The unit, bolstered by its strategic planning and performance, acquires additional financial resources at both national (e.g. ANR, INCa, FRM) and international levels, significantly augmenting its recurrent budget from Inserm and Université Paris Cité. The recurrent budget, amounting to 210 k€ per year (with contributions of 170 k€ per year from Inserm and 40 k€ per year from Université Paris Cité) forms the financial backbone of the unit. A strategic 60% of this budget is meticulously allocated for shared consumables, equipment maintenance, and management, ensuring the smooth operation and upkeep of the unit's resources.

To further bolster its capabilities, the unit effectively leverages external funding sources, which constitute approximately 2/3 of the total budget. This additional funding is a testament to the unit's excellence and reputation, allowing it to pursue ambitious projects and maintain cutting-edge facilities.

The distribution of resources, including the allocation for human resources, is overseen by the senior scientist who secures a grant, ensuring that each project is not only well-funded but also efficiently administered. As a result, the unit not only thrives in its current research environment but is also well-positioned to adapt and expand, driven by a sustainable and strategically allocated financial structure.

The seamless integration between basic scientists and clinicians is commendable.

Weaknesses and risks linked to the context

There is a notable insufficiency in permanent technical support across all teams, leading to an imbalance in the distribution of technicians and engineers. This uneven allocation not only affects the harmony and efficiency of team operations but also could potentially slow down the research progress due to limited technical assistance.

The unit's capability to nurture innovation and sustain its research momentum is compromised by the lack of young investigators with permanent positions and post-docs. This deficit might lead to a gap in fresh ideas, innovative approaches, and the latest scientific skills that young talents typically bring to research environments.

The absence of these vital roles could hinder the unit's competitive edge and its ability to keep pace with rapid advancements in the field.

The unit's reliance on external collaborations for the majority of its bioinformatics analysis indicates a significant vulnerability. The absence of in-house bioinformatics referents or a dedicated platform can lead to dependency on external entities, potentially affecting the confidentiality, timeliness, and customization of analyses. This reliance might also limit the unit's ability to rapidly respond to research findings or adapt to new bioinformatics methodologies and tools.

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

The organization and life of the unit are excellent with a marked enthusiasm among staff at each level.

Decisions regarding the management of financial resources are made collectively, with a democratic approach involving consensus among all team leaders during quarterly board meetings and an inclusive yearly laboratory council. This collaborative governance ensures that the financial strategy aligns with the unit's overarching goals and research priorities.

Several actions have been taken to improve gender equity, which is now better balanced. This includes co-chair position in Team 1, involvement of the unit in PEP Inserm program, a member of Team 2 as parity referent (2022) and a member of Team 3 promoted full professor position (2022). Moreover, since 2019, visiting speakers respected a parity rule.

Internal promotions are supported, e.g. promotion to a DR position in Team 1 and to IR position in Team 2 (2018). The unit acquired permanent position in technical staff: an engineer position has been obtained for Team 1 (AI) from Inserm in 2020 and for Team 2 (IE) from université Paris Cité in 2021.

Each team has a dedicated space for cell culture and specific experiments, the rest of the space is shared by all the teams (storage and common facilities).

The unit monitors Hygiene and safety (H/S) regulation application and psycho-social risks.

Electronic laboratory notebooks ensure data protection, which is assured in accordance to recommendation from Inserm and université Paris Cité.

The unit has effectively managed the Covid-19 pandemic crisis and settled up a 'Plan de Continuité d'Activité' (PCA) on March 2020.

Weaknesses and risks linked to the context

The unit is located in a very old building, this is detrimental for a good environment of work.

The problem of the gender balance at PI's level is persisting.

The functioning of the unit is negatively impacted by the institutional administration not too much reactive and not too much turned towards the unit's needs.

EVALUATION AREA 2: ATTRACTIVENESS

Assessment on the attractiveness of the unit

The unit's attractiveness is excellent. The excellent scientific productivity ensures gain in international visibility, reflected by invitation to attend international conferences as speakers, steering bodies, panels of experts and editorial boards. There is an excellent training in good laboratory practices, research integrity, bioethics, and care in the integration of foreign researchers. The fundraising capacities are excellent, mostly from national funding agencies (INCa, ANR, FRM) and participation to several PIA programs. Teams benefit from several IRSL core technological and bioinformatic platforms.

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

In the reporting period, team leaders and members of the unit have been regularly invited to international scientific meetings and workshops in the fields of Immunology, Haematology and Gastroenterology, including the 2018 Gordon Research Conference on Chemokines Cytokines, the 6th European Congress of Immunology (2021), the 11th International Workshop on Waldenstrom's Macroglobulinemia (2022), the Kyoto T cell Conference (2017), the 2019 FOCIS annual meeting, the 2019 EBMT annual meeting, and the NK-2019 Luxemburg International Symposium.

Team leaders are invited to join local and national steering and advisory bodies including IRSL, Inserm, Hcéres, ANR, French Society of Immunology, 'Cancéropôle Île-de-France', Institut Carnot OPALE, EBCNet, EFIS, FOCIS, EBMT, AFEMI, UEGF, IOBID. Team leaders are members of editorial boards of specialist journals (i.e. Frontiers in Immunology, European Journal of Immunology, Frontiers in Endocrinology, Oncoimmunology, Digestive and Liver Disease) and are invited as panel experts by national and European funding agencies (EHA, Czech Academy of Sciences, Worldwide Cancer Research) and international prizes (i.e. 'Fondation l'Oréal'-Unesco for Women in Science).

The unit has given particular attention to the implementation of rules and regulations ensuring good laboratory practices by all team members. Regular recording and traceability of experimental activities, in particular those based on human biological specimens are requested. Training on bioethics is offered. The unit seeks to keep an international environment through the recruitment of foreign students and post-docs in the context of international collaborative networks. The unit offers to the research and support personnel training programs (i.e., lab management, computer software skills, animal experimentation, website design, single cell analysis, imaging technology). The unit organizes of a seminar series in Immunology for external speakers, together with the ISRL seminar series to which each month two speakers from different units discuss their recent data.

In the reporting period, the unit's leaders have adeptly secured multiple grants, showcasing their strong scientific standing and collaborative capabilities. Nationally, they have coordinated and partnered in significant grants, including an ANR grant "Osteovalymph" with a total budget of 467 k€ (team's share: 252 k€), and an INCa grant "BM-Immune-MDS" with a total budget of 488 k€ (team's share: 380 k€). These efforts highlight their ability to attract substantial research funds. On the European front, their involvement includes partnerships in the MSCA H2020 "Oncornet" project, reflecting their commitment to international collaboration and high-impact research. The unit has also participated in various PIA programs such as Labex Lermit and IHU 2 THEMA, demonstrating its role in advancing scientific research on a national scale. Overall, the unit's successful grant acquisitions from various national and international funding agencies underscore its capability to conduct and lead high-quality research while fostering strong collaborations across the scientific community.

The unit provides core support to purchase and run technological platforms (cytometry, imaging, genomics, biodata centre), which are centralized within the mixed service unit Saint-Louis US53/UAR2030 unit.

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

Individual team leaders have not yet succeeded in being awarded with prestigious European funding schemes, including European Research Council (ERC) grants.

Organization of international conferences to improve the unit's visibility and attractiveness towards foreign researchers remains limited.

EVALUATION AREA 3: SCIENTIFIC PRODUCTION

Assessment on the scientific production of the unit

The scientific production is excellent. The unit exploits (i) multiple collaborations at local, national and international level, (ii) multiple complementary expertise among teams as well as collaborations with clinicians, and (iii) the access to biological and clinical samples/data. The teams have established effective links between basic research, translational research and clinical research, resulting in high-quality basic and translational research. This high-level research has led to publications in leading journals with a general audience (J. Exp. Med., PNAS, Sci. Transl. Med., Nat. Commun.), as well as in top-level specialty journals (e.g. Blood, Leukemia, Gut, Br. J. Dermatol., J. Immunol., Cancer Immunol. Res., J. Immunon. Ther. Cancer).

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

The unit's scientific output over the reporting period is based on solid theoretical and methodological observations, evidenced by 463 original articles (scientific and clinical), including 106 fundamental/translational studies. Among them, 98 original articles with last/first authorship have been published in leading journals with a general audience (J. Exp. Med., PNAS, Sci. Transl. Med., Nat. Commun.) or top-level specialty journals (Blood, Leukemia, Gut, Br. J. Dermatol., J. Immunol., Cancer Immunol. Res., J. Immunon. Ther. Cancer). The scientific output is commensurate with the unit's research potential, in terms of both staff numbers and categories. Moreover, it is evenly distributed between the teams. All junior research staff (doctoral and post-doctoral levels) contribute to this scientific output, with a total of 43 original articles with a PhD student or post-doctoral fellow as first or co-first author. More than ten articles involve members from several teams of the unit. The unit's scientific output also includes top-level co-publications with internationally recognized partners (Cell Rep., Blood Adv.).

Among these publications, two major achievements can be highlighted. The first one includes several groundbreaking studies providing novel mechanistic insights on CXCR4 signaling, notably the regulation of (i) the lymphoid potential of HSPC, (ii) the osteogenic fate of BM SSCs and (iii) PC homing, differentiation and function. The second one is the definition of a genetic control of human thymopoiesis in healthy adults, based on a very solid study involving 1 000 individuals.

In addition to these groundbreaking studies, the unit has produced important data on (i) the impact of the myelodysplastic syndrome associated *TET2* mutations on NK cell function and genome methylation (Nat. Commun.); (ii) the key role of the acetylation of the transcription factor PLZF in NKT differentiation (J. Immunol.); (iii) novel insights in T-cell mediated responses in Inflammatory Bowel Disease (Front. Immunol., Gut) as well as in the physiopathology of post-operative recurrence in Crohn's disease (APT, CGH, AJG, JCC). These studies strongly capitalize on the access to clinical samples linked to clinical data by the unit members as well as the use of challenging and original approaches, notably the implementation of co-culture models of human intestinal organoids and autologous mucosal lymphocytes; (iv) the identification of activatory (NKG2D) and inhibitory (NKG2A) receptors expressed on NK cells and CD8 T-cells as well as the ectonulcease CD39, the level of expression of which affects tumour progression and can be exploited to increase anti-cancer immunity (JITC, Gut), through the use of blocking antibodies; (v) new insights on the role of NK cells in response to melanoma and breast cancers (Cancer Immunol. Res., Front. Immnunol., JITC), and in particular, original observations outlining NK/ILC3 plasticity between tumour and metastatic lymph nodes and its impact on tumour growth (Oncoimmunol.); (vi) evidences of the great diversity of circulating and skin-derived Sézary cells in terms of maturation phenotype, molecular signature and cytokine/chemokine expression (Blood, Br. J. Dermatol.).

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

Some teams capitalize more on their links with clinicians and the cohorts they have set up than on carrying out mechanistic studies.

The usage of the 'HAL' platform as an open access resource is not well developed.

EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

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

The contribution of the unit to society is excellent. The unit has close contact with patients' associations. The three teams have registered a total of 6 patents (including promising methods to obtain lymphoid progenitors and innovative CXCR4 antagonists). With a total of 10 industrial partnerships (e.g. X4 Pharmaceuticals Sanofi-Aventis, Novo Nordisk, Innate Pharma) covering a wide array of research areas, the unit is fully committed to translate basic research into clinical applications. The team members have actively participated in initiatives aimed at the general public (e.g. open-door meetings with patients, program 'l'arbre des connaissances – apprentis chercheurs').

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 effectively leveraged its close ties with patients' associations related to allo-HSCT, haematology, and IBD to foster collaborative research and understand patients' needs directly. In terms of technology transfer and innovation, the unit has registered six patents, including promising methods to obtain lymphoid progenitors and innovative CXCR4 antagonists. These patents, along with ten diverse industrial partnerships with entities like X4 Pharmaceuticals, Sanofi-Aventis, Novo Nordisk, and Innate Pharma, underscore the unit's robust commitment to translating basic research into clinical applications. The partnerships cover a wide array of research areas, from lymphoid progenitor differentiation to immune response studies in leukemia and Crohn's Disease, indicating the unit's interdisciplinary strength and its potential for real-world impact.

Further detailing the unit's contribution to society, the team has been actively involved in patients' association activities, including those with the 'Association Laurette Fugain', 'Association François Aupetit', and 'Association Saint-Louis'. They have hosted pupils for observation training periods, demonstrating a commitment to inspiring the next generation. The team members have participated in initiatives aimed at the general public, such as open-door meetings with patients, the program 'l'arbre des connaissances – apprentis chercheurs' and scientific vulgarization efforts through various media outlets. For example, one team member (co-leader of Team 1) presented at 'Le langage des chimiokines' seminars and engaged with middle and high school students in Clamart.

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

While the unit's interactions with the general population through various initiatives are noteworthy, the critique points out that these actions are not very recent and could benefit from reactivation. This implies a need for a more consistent and updated approach to engaging with the broader public and maintaining the momentum of such interactions. Reactivating and citing more recent public engagement activities within the reporting period would not only demonstrate the unit's ongoing commitment to societal contribution but also enhance its visibility and impact.

ANALYSIS OF THE UNIT'S TRAJECTORY

The trajectory of the research unit is marked by a dynamic evolution and strategic foresight, aiming to consolidate its position at the forefront of scientific inquiry and innovation. The establishment of a single UMR as a 'Centre de Recherche' is a pivotal development, merging the strengths and resources of existing teams to foster a unified and synergistic research environment. This strategic move is anticipated to boost scientific productivity, facilitate interdisciplinary research, and enhance the unit's international visibility.

In terms of individual teams, Team 1 continues to delve into the chemokine-regulated interactions between lymphocytes and their microenvironment, building upon a strong foundation of past achievements. Similarly, Team 3 remains dedicated to advance our understanding of intestinal immunity in inflammation and cancer, leveraging its established expertise in oncoimmunology and mucosal immunity. Both teams, situated within the newly formed centre, are poised to exploit the collaborative environment and state-of-the-art technological platforms, including investments in pre-clinical investigations, imaging, flow cytometry, genomics, and data analysis.

Team 2 is navigating significant changes with the departure and retirement of key figures, marking a period of transition and opportunity. The arrival of new leadership and members signifies a reinvigorated focus on lymphocyte development, particularly within the context of the aging thymus and hematopoietic diseases. The restructuring of Team 2 is emblematic of the unit's adaptive and forward-looking nature, ensuring continuity in excellence while embracing new scientific directions.

The research trajectory is further characterized by an intense translational approach, bridging the gap between bench and bedside. This is evident in the unit's strong collaborations with clinical departments, participation in high-value patient cohorts, and commitment to clinical research. The integration of innovative statistical approaches for data analysis and the involvement in early therapeutic trials enhance the translational impact of the research conducted. The clinical component is a testament to the unit's commitment to improving patient care and health outcomes, with substantial partnerships and initiatives in diseases of significant societal impact such as haematological disorders, inflammatory bowel diseases, and cancer.

Overall, the unit's trajectory reflects a harmonious blend of continuity and change, with established teams building on their scientific strengths and new configurations adapting to emerging challenges and opportunities. The formation of the new research centre is a critical step in this journey, promising to catalyse scientific discovery, foster innovation, and translate research findings into meaningful clinical advances. This strategic evolution of the unit underscores its commitment to remaining at the cutting edge of scientific research and healthcare innovation.

RECOMMENDATIONS TO THE UNIT

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

The technical support should be reinforced for each team.

One out of three teams has men as PIs, the gender balance in each team has to be restored.

A support as bioinformatics referents/platform should be implemented.

The structural problem of the building where the unit is located has to be solved as soon as possible.

Administrative documents (e.g. PhD contracts) should be drafted in English to help foreign students.

Recommendations regarding the Evaluation Area 2: Attractiveness

The unit is encouraged to increase its international visibility through the participation to European-funded international doctoral programs schemes.

The strong expertise acquired over the years by the unit in the establishment of original primary bone marrow and thymic cultures as well as tumor organoids should be shared with the national and international scientific community via organization of workshops (e.g. EMBL).

The participation to ERC funding schemes is strongly encouraged given the leading position of team leaders in topics related to the role of the microenvironment in regulating healthy and pathological hematopoiesis as well as in solid tumor formation.

The strong translational axes of the unit could benefit from collaborations with strong basic research laboratories in the international arena to extend its visibility and complement the local know-how, with research activities, methodologies and approaches that are yet unfamiliar with the unit.

Recommendations regarding Evaluation Area 3: Scientific Production

The unit is encouraged to continue linking basic research, translational research and clinical research to further improve the overall qualitative impact of publications.

All teams are encouraged to sustain and/or strengthen basic research. This will particularly allow to better exploit all the data available in cohort studies.

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

The unit could plan new initiatives regarding public engagement. This might include seminars, participation in science festivals, increased media presence, or collaborative events with patients' associations. By doing so, the unit would strengthen its societal impact and public presence.

TEAM-BY-TEAM OR THEME ASSESSMENT

Team 1: Homeostatic and Pathological Chemokine-Regulated Interplays between Lymphocytes and their Microenvironment

Name of the supervisors: Mr Karl Balabanian & Ms Marion Espéli

THEMES OF THE TEAM

Team-1 studies, in primary cultures, and human biological specimens, the functional consequences of the interaction between different hematopoietic cell types and the surrounding bone marrow (BM) microenvironment embedded within spatially-resolved anatomical niches. In addition, the team investigates BM microenvironmental alterations linked to onset of myeloid neoplasms. The team has developed a mouse model to study the effects of constitutive activation of the chemokine receptor CXCR4 in hematopoietic lineage commitment, plasma cell homeostasis and osteogenesis, which has led to a number of original observations. In the field of human myeloid neoplasms the unit has unravelled the impact of TET2 mutations on T- and NK-cell tumour immune surveillance in the BM.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous recommendations were the following:
1. The unit should actively pursue high profile publications.
Team 1 has addressed this point increasing quality of its publications in top notch specialist journals.

2. The unit as a whole has poor gender equity, although recent recruitments are well balanced.
Gender balance has been carefully considered, with the appointment of a new team head and incorporation of a new senior team member from former Team 3.

3. The future situation of the unit beyond the 5-year plan needs to be considered (i.e., when the current director is due to retire). Within the next 2-3 years a decision should be taken to either pursue a merger with the other unit on site, or to train a new director (i.e. appointing a deputy director).
Attention to the future of the unit is witnessed by the nomination of one of the leaders of Team 1 as Deputy Director.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	1
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	1
Sous-total personnels permanents en activité	**4**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	1
Post-doctorants	2
Doctorants	7
Sous-total personnels non permanents en activité	**10**
Total personnels	**14**

EVALUATION

Overall assessment of the team

The overall assessment is excellent to outstanding. The scientific productivity is excellent to outstanding in top-ranking specialist journals (e.g. Nat. Commun., Blood, J. Exp. Med. and PNAS). This translates into steady invitations to international conferences, joining of editorial boards and participation to panels of experts in funding bodies. The team has secured excellent funding through competitive national calls (i.e. 2 ANR, 1 INCa and 1 FRM grants as PIs) and PIA programs (Labex LERMIT, IHU2 THEMA, Institut Carnot OPALE, and FHU PROTHEE), ensuring the recruitment of thirteen PhD students. Team attention to research integrity, bioethics, human sample processing, open access publication is excellent to outstanding. Links to industry, valorisation of the results, and cooperation with local, national and international hospitals are excellent.

Strengths and possibilities linked to the context

The team has built in the reporting period a strong reputation in the field of molecular haematopoiesis in health and disease. In particular, state-of-the-art and human models have led to clinically-relevant findings in the field of early haematopoiesis, plasma cell biology and pathology, as well as in myeloid leukemia tumour immuno surveillance. These three research axes share the common interest of the team in studying the crosstalk between normal and malignant hematopoietic cells and the bone marrow microenvironment.

The team published 101 research articles, including 16 as first/corresponding author in top-ranking specialist journals (i.e., Blood, Nat. Commun., PNAS, Leukemia) has improved international visibility, attracting foreign researchers recruited at the post-doc level as well as stimulating clinical and research collaborations with international centres (i.e., NIH, BRIC), on a solid steady background of strong collaborations with national reference centres in haemato-oncology, pathology and immunology.

Maintenance of high-quality research activity is guaranteed by five tenured researchers, supported by three full-time engineers/research assistants, supervising a dynamic number of PhD students (13 for the reporting period) and few post-doctoral fellows.

Consistent high-level funding of the team has been secured through several grant applications awarded in response to competitive calls mostly by national funding bodies, where team leaders acted as coordinators (2 ANR, 1 INCa and 1 FRM grants). Team leaders also participated to PIA programs as axis coordinators (Labex LERMIT) or partners and steering committee members (IHU2 THEMA program, Institut Carnot OPALE program, and FHU PROTHEE program).

Excellent valorisation of the studies is witnessed by the filing of four patents and several partnerships with the industry (i.e. Idorsia, X4 Pharmaceuticals, Sanofi-Aventis).

Genetic and functional studies to identify microenvironmental and immunological defects associated to the pathogenesis of myeloid neoplasms, WHIM syndrome and Waldenstroem macroglobulinemia witness the commitment of the team to translate basic research findings into the clinical setting.

Weaknesses and risks linked to the context

Organization of international conferences (i.e. EMBO workshops) to increase international visibility on topics related to bone marrow haematopathology and microenvironment for which the team is well acknowledged represents a strong yet largely missed opportunity to enhance international attractiveness.

The team has not placed significant efforts to increase the attractiveness towards international researchers at different levels of their career.

Despite the excellent productivity of the recent years and the strong name recognition in the field of bone marrow immuno/haematopathology, application to Advanced European Research Council grants by the team leaders seems yet not pursued.

The connection to the clinical community is strong yet but could be improved given the original preclinical bone marrow culture models developed by the team.

The attention of team members to science communication activities to the large public is intangible.

Analysis of the team's trajectory

The team has developed so far a robust research program focusing on the interaction between normal/malignant hematopoietic cells and mesenchymal stromal cells (MSC) in the bone marrow. The team's work has assigned to the CXCR4/CXCL12 axis a relevant function in regulating the fate of MPP4 multipotent progenitor cells, homeostasis of plasma cells, and osteogenesis. In the next mandate, the team plans to explore how constitutive CXCR4 signalling impacts the homing of MPP4 and plasma cells to specific bone marrow niches, thereby affecting MPP4 development and long-term plasma cell survival.

Utilizing *in vitro* and *in vivo* studies, advanced *in situ* cell imaging, gene expression studies (including single-cell RNA sequencing and spatial transcriptomics), and flow cytometry, the team plans to: 1) examine the repertoire of receptor/ligands controlled by the CXCR4/CXCL12 axis, necessary to sustain localized communication between bone marrow MSC and hematopoietic cells; 2) assess how enhanced CXCR4 signalling affects the metabolic and transcriptional rewiring of mis-localized MPP4 cells; 3) investigate the influence of dysregulated CXCR4 on aberrant differentiation of age-associated B cells into plasma cells in mouse models of WHIM and Waldenstrom Macroglobulinemia. The team also aims to monitor age-associated transcriptional changes in aging bone marrow long-lived plasma cells and interacting leptin-receptor positive MSC at single-cell resolution. The goal is to determine if progressive hematopoietic exhaustion is linked to deregulated interactions between accumulating plasma cells and MSC's, which in turn may negatively affect development of MPP4 cells into the lymphocyte lineage.

A second research axis of the team will focus in the next mandate on defining molecular and phenotypic features of malignant T cells and normal immune cell subsets in the skin and blood of Sezary Syndrome (SS) patients. Longitudinal studies on SS patients treated with anti-CCR4 (and possibly anti-CCR8) therapeutic antibodies will explore the impact of the treatment on rewiring of the skin microenvironment in favour of a possible enhancement of anti-tumour immunity. The investigations will be based on different types of analyses, which include scRNA-seq and spectral flow cytometry performed on immune, stromal, and malignant cells retrieved from affected skin and from the circulation. Finally, the team plans to assess the impact of TET2 mutations on NK cell development in the context of myelodysplastic syndromes (MDS). The team will also explore how MSC from the bone marrow of MDS patients and aged individuals with clonal haematopoiesis possibly interfere with normal haematopoiesis, interfering with lymphopoiesis and NK cell development while favouring malignant expansion of the myeloid compartment.

RECOMMENDATIONS TO THE TEAM

The team should place efforts to increase its attractiveness towards international researchers interested to join them in particular at the level of post-doc fellows.

Team leaders have acquired the proper scientific status to be awarded with European funding schemes including European Research Council grants.

Participation in structures created by the PIA is encouraged.

Organization of international workshops and practical courses centred for instance on preclinical organoid/mixed bone marrow cultures to study normal and malignant haematopoiesis will help consolidate the team's leadership in studies on the crosstalk between hematopoietic cells and the bone marrow microenvironment.

The strong expertise built by the team over the years in the establishment of advanced preclinical bone marrow culture models and in generation of clinically relevant mouse models centred around the CXCR4/CXCL12 axis, should be fetter exploited to attract the interest of haematologists, clinical immunologists and rheumatologists at both the national and international levels, allowing stronger visibility and greater fund raising.

More attention to the public outreach of discoveries made by the team is recommended.

Team 2: Thymic function and development

Name of the supervisors: Mr Antoine Toubert & Mr Kamel Benlagha

THEMES OF THE TEAM

Team 2 is studying thymic function and development in the overall topic of the unit looking at mechanisms governing the organization of niches in various tissues and organs, regarding the crosstalk between lymphoid immune cells and their environment at steady state of pathological situations. In this regard, the team has developed two axes led individually by two PIs.

The first group has developed an expertise in the field of T Cell repertoire and thymic function in human immunology with approaches of excision circles (TREC) quantification, as molecular markers of thymic function, with particular focuses on the genetic control of thymopoiesis in healthy humans, the effect of aging in thymic regeneration and the immune reconstitution in clinical settings such as allogenic HSCT, autologous HSCT in autoimmune diseases and gene therapy for Wiskott-Aldrich.

The second group has a strong expertise in the study of iNKT cells in murine models and in humans, in particular the study of the impact of TCR-CD1d ligand recognition in iNKT development and the role of the regulation of PLZF, key transcription factor downstream to TCR signalling.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Regarding the production and activities, the recommendation to focus more on quality than quantity of publications and utilize more the clinical cohorts was clearly taken into account. The publications are of a very high level, clinical cohorts have been utilized as much as possible.

Regarding the organization and life of the team, following the retirement of an IE (Université Paris Cité) in 2019, it has been possible to recruit an engineer (IE Université Paris Cité) under a permanent position in 2021. The gender issue is well taken into consideration since the head of the team is at parity. Two technicians from AP-HP, moved to the routine laboratory, have been replaced by a non-permanent staff funded by external ANR grants (ANR RANKLThym 2019 and ANR Hu-Thy-L 2021).

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

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

EVALUATION

Overall assessment of the team

The overall assessment is excellent. The general topic of the team is well included and perfectly fits in the general orientation of the whole unit. The scientific production is excellent with articles published in high-profile journals (e.g. Sci. Transl. Med., Gut). With a rare expertise on thymopoiesis well-recognized at the highest international level, the attractiveness of the team is excellent. It is well funded with several grants (e.g. ANR with one grant as PI), well implicated in PIA programs (e.g. IHU2 THEMA, Institut Carnot OPALE, RHU IRIS, Labex 'Milieu Intérieur' and Transplantex) and has a significant level of external collaborations. With one patent and industrial partnerships for three clinical trials, the valorisation of the results and links to industry are excellent.

Strengths and possibilities linked to the context

The expertise of the team is recognized at the highest international level, in the field of thymopoiesis, as well as NKT biology. This led to the publication of 51 original articles and eight invited reviews in e.g. Sci. Transl. Med., Gut, Blood Adv., Semin. Immunopathol., J. Immunol. Among them, eleven articles are published as senior or co-senior author and seven with a PhD student or post-doc fellow as first or co-first author. The article in Sci. Transl. Med. (2018), emphasizing the original definition of a genetic variation associated with the level of thymopoiesis in humans, may be considered as a real scientific breakthrough. This was highlighted in a press release of Pasteur Institute and selected by F1000.

The expertise in thymic biology is of particular interest regarding its impact in knowledge and in human immune diseases, and is shared by only a few teams worldwide.

The team has secured a significant funding level during the reporting period. At the national level, it has obtained an ANR grant as PI (230 k€ out of a total of 676 k€), including external partners from Paris and Marseille, and is partner of other grants (ANR grant Marseille, UPC grant with Inserm U1151/INEM and Necker Hospital). At the international level, the team is partner of a FP7 ERA-NET program and a COST action.

The team is well implicated in PIA programs, participating to the IHU2 THEMA, Institut Carnot OPALE, strongly involved in the Labex 'Milieu Intérieur' (from its start in 2010), the RHU IRIS and the other Labex Transplantex. For each contribution, the team brought its rare expertise in the field of thymic function.

Both PIs are involved in many collective actions and missions (e.g. chief editor of Frontiers Immunology, Doctoral School HOB, president of the IRSL scientific board, director of FOCIS centre of excellence, Hcéres advisor, SFI board member).

The team has participated to exchange and training program of three foreign students, one PhD student from Brazil, one in the FAPESP/UPC exchange program and finally one from Italy for an MD training exchange. They got one award from EBMT in 2019.

The team has deposited one patent on its field of expertise regarding the common genetic variations at the TCRA-TCRD locus control thymic function in humans. It has secured several industrial partnerships for three clinical trials.

Weaknesses and risks linked to the context

The team is rather small, constituted of a few permanent senior researchers, with some of them close to retirement.

It is not obvious how both axes of Team 2 have performed collaborative work.

The number of PhD students is limited.

The team will be confronted to two major moves of the PIs (mobility and retirement). The future exercise will have to pay a particular attention to the succession phase, but is already clearly addressed in the trajectory.

Analysis of the team's trajectory

Team 2 will evolve significantly for the next mandate with major changes related to the move and the retirement of the two former PIs. The future team will be led by a Professor of Immunology at Université Paris Cité and researcher at Pasteur Institute.

Thus, the team will work on two axes: 1/ ILC development and biology and 2/ Thymic function. The future PI recently successfully applied to the creation of a joint Pasteur Institute/Université Paris Cité team that will clearly reinforce this new organization by keeping her link with Pasteur Institute. One full-time researcher (CR Inserm) will join the team with an expertise in ILC, T and B development, allowing a link with the second axis on thymopoiesis.

The first axis will focus at understanding the dialogue between innate lymphoid cells and their microenvironment, namely the bone marrow and peripheral organs. They will characterize the role of the molecular and cellular interactions between the BM stroma and their interacting ILC2P/ILC2 but also the co-evolution of ILC2 and their BM niches during aging and inflammation.

The second axis remains on the thymic function and will aim at defining the parameters governing the human thymic function in healthy conditions and during aging, within the labex 'Milieu intérieur': 1/ Analysis of the resampling of MI donors 10 years after the initial sampling; 2/ Analysis of neonatal set-up of the adaptive immunity (thymic function and B-cell neogenesis) in an international collaboration on very rare cohorts followed at Karolinska Institute; 3/ Defining parameters of thymopoiesis and SNP impact in a healthy human cohort of Asian genetic background. A second aim will be to define the impact on thymopoiesis of the SNP rs2204985 common genetic variation at the TCRD-TCRA locus. A third aim will concern the thymic aging in the context of clonal haematopoiesis of indeterminate potential (CHIP).

RECOMMENDATIONS TO THE TEAM

The team should attract new senior scientists, PhD students and/or and post-docs on such an important topic on thymopoiesis.

The team should define more precisely how both axes (ILC and thymus) could crosstalk.

The scientific strategy should be clearly defined to keep both axes balanced in the team and to secure the thymus axis after retirement of the PI expert in the field.

The committee encourages the promising approach on organoids and genome editing to go further.

The committee encourages to reinforce the workforce on thymus function.

Team 3: Intestinal Immunity in Inflammation and Cancer

Name of the supervisors: Mr Matthieu Allez & Ms Anne Caignard

THEMES OF THE TEAM

Team 3 combines expertise on the immune system in inflammation and cancer. It focuses on the role of lymphoid cells, such as T and NK cells, in human pathologies in peripheral organs that are the skin and the intestine.

One theme is focused in the physiopathology of Inflammatory Bowel Disease. It also exploits their knowledge and know-how on this topic to study the immune response in colorectal cancer, with the aim of finding new therapeutic approaches based on the use of antibodies targeting molecules involved in tumour progression. A second theme is to study the role of innate immune cells in cancer immunosurveillance, notably in breast cancer and melanoma. The team develops a third theme on the study of cutaneous T-cell malignancies and the interplay between blood and skin components.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team has taken into account the recommendation made by the previous committee, notably a better exploitation of the clinical cohorts and patients' samples. This led to high-quality publications in specialized journals (e.g. Gut, JITC, Blood).

In terms of unit's organization and life, the team has made efforts to improve the balance between men and women in management positions. However, with the new organization of Team 3, linked to the departure of two women PIs from Team 3 (due to the retirement of one PI and the moving of another PI to Team 1), management will be assumed by two men.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	5
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	1
Sous-total personnels permanents en activité	**8**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	2
Post-doctorants	0
Doctorants	2
Sous-total personnels non permanents en activité	**4**
Total personnels	**12**

EVALUATION

Overall assessment of the team

The overall assessment is excellent. The team has an excellent complementarity between researchers and clinicians. The scientific production is excellent with articles published in speciality journals (e.g. Gut, Oncoimmunology, Br. J. Dermatol., JITC, Lancet Hematol., Lancet Oncol.) in leading position. The attractiveness is excellent with a high fundraising capacity (e.g. 2 ANR grants with 1 as PI and 2 INCa grants with 1 as PI) and a nationally and internationally recognized expertise on the immune system in inflammation and cancer.

The close relationship with hospital departments to provide patients' samples associated with clinical data enables the team to carry out meaningful translational research. It has also established excellent industrial partnerships to translate their scientific outputs into novel therapeutic approaches.

Strengths and possibilities linked to the context

The team is very well-recognized for its expertise on the immune system in inflammation and cancer. It has produced 311 scientific articles over the reporting period, mostly in journals of Immunology, Oncology, Gastroenterology and Dermatology specialities as PI (e.g. Front. Immunol., Gut, Oncoimmunology, Br. J. Dermatol.). Taken together, the team members have published 71 original scientific articles as first and/or last author (e.g. Frontiers Immunol., Gut, Oncoimmunology, Br. J. Dermatol., JITC, Lancet Hematol., Lancet Oncol.) and 240 as collaborative papers including original articles and reviews.

The team has an excellent complementarity between the different PIs and clinicians. The access to biological and clinical samples/data and the establishment of different cohorts enable the team to carry out meaningful translational research. It has also implemented challenging and original approaches based on co-culture models of human intestinal organoids and autologous mucosal lymphocytes.

The team has done very well in attracting funding during the reporting period (2.2 M€ in total) in international (600 k€, Helmsley Charitable Trust Research Program: IBOT 3IBD Overtime, as coordinator) and national (1.1 M€) calls as well as from valorisation and industrial partnerships (Novo Nordisk, Innate Pharma, Celgene) (500 k€). At the national level, the team coordinated two grants (ANR JCJC and INCa), participated to two others as partner (ANR PRC and INCa PL-BIO). Other national funding was from 'Société Française de Dermatologie', 'Cancéropôle Emergence', ARC, Fonds AMGEN.

The team has trained eight PhD students.

The team has organized several international meetings on Inflammatory Bowel Disease (IBD) (an annual Franco-Romanian IBD meeting since 2014, and the International Organization for the study of IBD in 2022).

All the PIs participate to national and international steering bodies (e.g. REMIND group, United European Gastroenterology Federation, International Organization of IBD, IOIBD, evaluation committees for ANR and Hcéres, board member of the SFI).

Weaknesses and risks linked to the context

The team is not involved in structures created by the PIA.

At the end of 2022, only two PhD students were still present in the team.

No post-doctoral fellows have been trained.

There is an imbalance between the number of PH (8) and DR (1)/CRCN (1) Inserm researchers.

Although the team has done excellent work, they have most published in journals of their main specialities.

They published work in generalist journals (i.e. Nat. Commun.) including studies done in collaboration with members of the other teams of the unit but these articles are not signed as first and/or last author.

Analysis of the team's trajectory

The team will evolve due to the departure of two PIs, and will be led by two PIs. It will refocus its research interests in the study of the immune system in inflammation (IBD) and colorectal cancer (CRC). It will continue to exploit (i) the access to the different patients' samples associated with clinical parameters and biological biobanking and (ii) its expertise in complex cellular system, based on the co-culture of intestinal organoids with mucosal autologous T-cells, the latter being a very valuable tool enabling collaborations with pharmaceutical companies. The research will be organized into two different but related research axes focused on:

- the study of T-cells in the physiopathology of IBD, through the assessment of (i) autoreactive T-cell clonal expansion, (ii) lympho-epithelial interactions in IBD. This axis will be co-coordinated and has already specific funding (ANR JCJC grant).

- leveraging mucosal T-cell biology against colorectal cancer, by (i) assessing the potential immunomodulatory role of KLRG1 in primary and metastatic CRC and (ii) modulating the tumour specific T-cell clones. This axis will be co-coordinated and has potential socioeconomic impact. It has already benefited from specific funding (Innate Pharma, INCa PL_BIO).

These lines of research will build on the team's published work, and the sharing of knowledge and know-how will enrich both themes.

RECOMMENDATIONS TO THE TEAM

The gender balance in senior management positions should be restored.
The team should participate in structures created by the PIA.
The team should acquire the means to develop more fundamental research.
The team should better balance the number of clinicians and full-time researchers.

CONDUCT OF THE INTERVIEWS

Date

Start: 11 December 2023 at 08:30

End: 11 December 2023 at 18:00

Interview conducted: online

INTERVIEW SCHEDULE

8:25-8:40	**Hcéres committee meeting**
	Closed-door meeting
8h40-8:45	**Hcéres rules and procedures *by M. Mercier-Bonin***
	Public session (all unit members)
8:45-9:15	**Scientific and administrative presentation of the unit**
	15 min. Overall presentation of the unit (including unit's trajectory) *Antoine Toubert*
	15 min. Discussion
	Public session (all unit members)
9:15-10:45	**Scientific presentations by team leaders**
	20 min presentation (including team's trajectory) + 10 min discussion
	Team 1 Karl Balabanian
	Team 2 Antoine Toubert
	Team 3 Matthieu Allez
	Public session (all unit members)
10:45-11:00	**Committee debriefing and break**
	Closed-door meeting
11:00-11:30	**Meeting with ITAs (in French)**
	In the absence of any managing staff
11:30-12:00	**Meeting with researchers**
	In the absence of any managing staff
12:00-12:30	**Meeting with post-docs and students**
	In the absence of any managing staff
12:30-13:15	**Lunch break**
13:15-13:55	**Meeting with institutions' representatives: Université Paris Cité & Inserm**
	Closed-door meeting
13:55-14:15	**Committee debriefing**
	Closed-door meeting
14:15-14:55	**Meeting with the Director & Deputy director of the unit**
	Closed-door meeting
14:55-15:10	**Break**
15:10-18:00	**Committee debriefing & redaction of the final report**
	Closed-door meeting
18:00	**End of the interview**

GENERAL OBSERVATIONS OF THE SUPERVISORS

Université Paris Cité

Le Président

Paris, le 8 février 2024

HCERES
2 rue Albert Einstein
75013 Paris

Objet : Rapport d'évaluation de l'unité **DER-PUR250024168 – Emily - Écotaxie, microenvironnement et développement lymphocytaire**

Madame, Monsieur

L'Université Paris Cité (UPCité) a pris connaissance du rapport d'évaluation de l'Unité de Recherche **EMily - Écotaxie, microenvironnement et développement lymphocytaire**
Ce rapport a été lu avec attention par la direction de l'unité, qui a identifié des erreurs factuelles sur les tableaux d'effectifs (cf version corrigée par le Directeur de l'unité, Antoine Toubert, ci-jointe), la vice-doyenne recherche et le doyen de la Faculté de Santé d'UPCité qui ont noté qu'il manque le nom du président en première page (M. Matteo Iannacone) et que le doyen Matthieu Resche-Riggon est étiqueté du titre de civilité Ms (à corriger par M.), par la vice-présidente Recherche d'UPCité et par moi-même.
Je vous remercie de veiller à la correction de ces erreurs factuelles.

Nous souhaitons, avec le doyen de la Faculté de Santé, souligner qu'Emily, unité dont les thématiques de recherche sont orientées sur l'immunologie et l'hématologie, sera un des éléments constituants du futur centre de recherche IRSL où ses thématiques s'intègreront parfaitement. Cette création de centre de recherche, accompagnée de profondes restructurations des équipes constituantes, a été accompagnée par les tutelles après avis d'un scientific advisory board. Ce centre augmentera la lisibilité, la visibilité et le rayonnement de la recherche sur le site de Saint Louis et plus globalement au sein de l'université.

En remerciant le comité pour la qualité du rapport, je vous prie d'agréer, Madame, Monsieur, l'expression de ma considération distinguée.

Édouard Kaminski

Présidence

Référence
Pr/DGDRIVE/2023

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