Research evaluation

EVALUATION REPORT OF THE UNIT

MI2 - Inflammation, microbiome, immunosurveillance

UNDER THE SUPERVISION OF THE FOLLOWING ESTABLISHMENTS AND ORGANISMS:

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

EVALUATION CAMPAIGN 2024-2025
GROUP E

Rapport publié le 11/02/2025

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

Chairperson:	Mr Matteo Iannacone, San Raffaele Scientific Institute & University, Milan, Italy
Experts:	Ms Agnès Castan Institut national de la santé et de la recherche médicale – Inserm, Grenoble(representative of supporting personnel) Ms Hélène Fenet, université de Montpellier (representative of CNU) Mr W.Florian Fricke, University of Hohenheim, Stuttgart Mr Jérémie Gautheron, Inserm, Paris Ms Elodie Segura, Inserm, Paris (representative of CSS Inserm)

HCÉRES REPRESENTATIVE

Ms Sophie Ezine

REPRESENTATIVES OF SUPERVISING INSTITUTIONS AND BODIES

Mrs Anne-Hélène Monsoro-Burq, Université Paris Saclay
Mr. Philippe Arhets, Inserm
Mr. Frederic Altare, Inserm
Mr. Eric Deutsch, Faculté de Médecine
Mr. Elias Fattal, Faculté de pharmacie

CHARACTERISATION OF THE UNIT

- Name: Inflammation, microbiome, immunosurveillance
- Acronym: MI2
- Label and number: UMRS996
- Composition of the executive team: Mrs Françoise Bachelerie, Director of the unit

SCIENTIFIC PANELS OF THE UNIT

SVE Sciences du vivant et environnement
SVE6 Physiologie et physiopathologie humaine, vieillissement

THEMES OF THE UNIT

The MI2 unit is a well-structured organization that integrates fundamental and translational research across three teams with distinct focuses: viral persistence, immunotoxicology, and liver disease. This multidisciplinary approach supports both scientific innovation and clinical relevance.

HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

The UMRS996 "Inflammation, Microbiome and Immunosurveillance" is a mixed research unit created in 2010 by Inserm and Paris-Saclay sud university directed by Dr. Dominique EMILIE (PU-PH) until February 2011. Between 2011 and 2014, the direction was headed by Marc Pallardy (PU, head of team 2) together with Françoise Bachelerie (DR1 Inserm, head of team 1). Since the last two contracts (2015-2019; 2020-2025), Françoise Bachelerie is the head of the unit. The unit comprises three teams and until July 2022 they were located on two different sites. Two of them were located in Clamart near Antoine Béclère hospital and the other one in the Faculty of Pharmacy of Chatenay-Malabry. Since 2022 the unit is now implanted on a unique site of the Faculty of Pharmacy in the Henri Moissan building in Orsay. The unit is now in close proximity to scientific institutes and renowned high-schools as well as academic and private research and development departments.

RESEARCH ENVIRONMENT OF THE UNIT

The unit is well integrated to its local environment (graduate School (GS), Health and Drug Sciences (HeaDS) and Life Science and Health (LSH)) by participating to the promotion of the platforms and interactions between laboratories. It si involved in developing multidisciplinary programs (Healthi) and is steering the Structure Fédérative de Recherche Institut Paris-Saclay and a service unit comprising eleven technical platforms. The unit is affiliated to the doctoral school "Innovation Thérapeutique du Fondamental à l'appliqué" (ED569). S. Kerdine-Römer is the head of the pharmacology/toxicology section. Several members of the unit have strong link with the clinical structures (Hôpital du Kremlin-Bicêtre, Ambroise Paré, Bichat- Claude Bernard and Antoine Béclère). Team3 is participating in the FHU (Fédération Hospitalo-universitaire) Hepatinov and FHU PaCEMM. The MI2 lab also participates to scientific networks "Investissements d'avenir programs", in PEPR "Biotherapies et production de biothérapies innovantes" and in IHU Prometheus. The unit benefits from the supports of the SATT (University Paris-Saclay) and Inserm transfert or Direv to promote the development of their research. Notably, a patent was deposited in 2024 by team 3 on protective bacteria to treat metabolism liver diseases. Team 1 has elaborated a pilot study to develop a preclinical model in mice on humanising the skin-immune system.
At the institutional levels, several lab's members are part af scientific boards and steering committees of Inserm and University Paris-Saclay. Team 3 is involved in the scientific transversal program "Microbiote" launched by Inserm, which aims to create a network to respond to PEPR call.

UNIT WORKFORCE: in physical persons at 31/12/2023

Catégories de personnel	Effectifs
Professeurs et assimilés	6
Maîtres de conférences et assimilés	11
Directeurs de recherche et assimilés	2
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	12
Sous-total personnels permanents en activité	**31**
Enseignants-chercheurs et chercheurs non permanents et assimilés	2
Personnels d'appui non permanents	2
Post-doctorants	2
Doctorants	14
Sous-total personnels non permanents en activité	**20**
Total personnels	**51**

DISTRIBUTION OF THE UNIT'S PERMANENTS BY EMPLOYER: in physical persons at 31/12/2023. Non-tutorship employers are grouped under the heading "others".

Nom de l'employeur	EC	C	PAR
U PARIS SACLAY	17	0	6
Inserm	0	2	5
AUTRES	0	0	1
Total personnels	**17**	**2**	**12**

GLOBAL ASSESSMENT

The MI2 unit is a well-structured organisation that integrates fundamental and translational research across three teams with distinct focuses: viral persistence, immunotoxicology, and liver disease. This multidisciplinary approach supports both scientific innovation and clinical relevance.

Scientific Production: Very Good
The unit's scientific output includes approximately 250 articles, with a breakdown as follows: Team 1 produced 95 articles, Team 2 contributed 97, and Team 3 added 58. The unit published 49 original articles as the primary investigator in both general and specialty journals, including notable publications in *Nature Communications*, *PNAS*, *Cell Reports*, *Blood*, *Gut* and *Scientific Reports*. External collaborations have yielded impactful work published in prestigious journals, such as in *Nature Immunology*, *Nature Communications*, and *Immunity*. Each team has produced valuable scientific highlights, underscoring their respective strengths:

- **Team 1**: Key findings include the characterisation of CXCR2 mutations in patients, insights into DC subset activation in WHIM syndrome, and therapeutic developments for autoimmune skin lesions.
- **Team 2**: This team has pioneered understanding of neuromuscular blocking agent-induced anaphylaxis and identified T-cell epitopes relevant to allergy research.
- **Team 3**: Noteworthy contributions include advancements in pectin-based treatment for liver lesions and bile acid modification pathways, with implications for gut-liver axis research.

Attractiveness: Excellent
The MI2 unit has proven highly attractive for recruitment, training, and public recognition. The successful recruitment of an Inserm Chair, two "Equipe FRM" labels, and nine ANR grants (five as coordinators) illustrate its appeal. The unit also participates in several prestigious programs, such as the Labex Lermit, FHU Hepatinov and PaCEMM, and IHU Prometheus (2023). Members contribute significantly to public expertise through national and international roles, including collaborations with ANSM, Anses, Hesi, Efsa, and WHO. The unit's training efforts are robust, with 23 PhD students having defended and foreign students welcomed through Erasmus and other partnerships. While the overall attractiveness of the unit is high, sustained efforts in staff retention and strategic recruitment will be essential as senior researchers approach retirement.

Valorisation: Excellent to **outstanding**
With a strong focus on translational research, the MI2 unit has established long-term collaborations with the clinical sector, including partnerships with various regional hospitals. The unit actively pursues technology transfer, working with SATT Paris Saclay to promote innovation through programs like PhD transfer initiatives and maturation projects. The unit has secured eleven industry-funded programs with companies like Servier and Solvay, and it has developed partnerships with fourteen pharmaceutical, chemical, and biotech companies. Collaborative projects often support PhD grants (7 Cifre), and three patents have been filed, covering innovations in skin models, immune system integration in preclinical models, and treatment methods for metabolic diseases. Additionally, Team 2 contributed to an antibody validation program with NIBSC under the WHO's guidance. A start-up is also underway to develop a topical treatment for lupus-related skin lesions. The unit's valorization efforts are further complemented by its participation in learned societies and public outreach through media, radio, and blogs.

Assessment of Teams:

- **Team 1 –Excellent**: Team 1 leads with impactful work on viral persistence and preclinical model development. Its achievements are well-aligned with the unit's mission, and it significantly contributes to the MI2's reputation.
- **Teams 2 and 3 – Very Good to Excellent**: Both teams contribute valuable work in immunotoxicology and microbiome studies, respectively. However, limitations in technical resources and visibility of the scientific production diminished their overall impact.
- **Conclusion: Overall, the MI2 unit is rated as Very Good to Excellent**. While each team effectively supports the unit's objectives, a more integrated approach and an emphasis on publishing in higher-impact journals could enhance its global reputation. Enhanced inter-team collaboration, strategic recruitment and retention, and a broadened approach to public dissemination will be critical for MI2's sustained growth and international recognition.

DETAILED EVALUATION OF THE UNIT

A - CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

The unit has partially addressed the recommendations related to scientific production and visibility. While efforts have been made to maintain scientific output, publishing in high-impact journals has proven challenging, as highlighted by the unit. Interruptions due to the health crisis and the relocation to Orsay significantly affected research timelines, particularly for PhD students, making it difficult to achieve this objective. Despite these obstacles, the unit remains committed to improving its visibility and continues to strive toward publishing in journals with a broader audience. The recommendation to increase patent filings has been successfully followed, with several patents filed during this mandate, indicating progress in leveraging industry collaborations to enhance intellectual property development.

For the unit's organization and life, no specific recommendations were made, as management was deemed excellent. Regarding scientific strategy and projects, the unit has made progress in refining its scientific priorities. This is evident from the successful acquisition of additional funding from the ANR and EU, which supports the continuation and expansion of its projects. The unit has also taken concrete steps to recruit new permanent full-time researchers. A significant achievement was the recruitment of a fellow for an Inserm Chair, despite previous unsuccessful attempts to attract candidates. This strategic hire is expected to contribute significantly to the unit's development.

The unit has also addressed the recommendation to optimize its integration with clinical research by maintaining strong collaborations with regional hospitals and preparing for the opening of the new Paris-Saclay hospital. The appointment of team 3 leader as head of the hepato-gastroenterology department in the merged hospitals, along with the integration of new doctors from Longjumeau Hospital into Team 3, positions the unit favorably for enhanced interactions between clinical practice and research activities.

B - EVALUATION AREAS

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 very good to excellent. For the unit as whole, they encompass timely, scientifically interesting and clinically relevant topics. However, a stronger integration of the team's individual objectives is needed to generate synergistic effects, e.g. through collaborations on overlapping research topics, such as microbiome components.

Assessment on the unit's resources

The unit's resources are very good to excellent, with access to shared local technologies, platforms and personnel. Funding through national programs, private foundations and industrial partners is excellent, but omics and bioinformatics support from within the unit is limited. Resources are expected to further improve after the completed relocation and establishment of the unit in Paris-Saclay.

Assessment on the functioning of the unit

The assessment of the functioning of the unit is good to very good. Regular meetings are organised with all teams members. However there is a disparity in the quality of communication within the teams that could be improved, in order to better relay information.

1/ The unit has set itself relevant scientific objectives.

Strengths and possibilities linked to the context

The unit has been working together since 2015 to first establish and then adapt separate but linked and convincing scientific programs. These are related to immune, infectious and inflammatory diseases and include clinically relevant objectives related to viral persistence (Team1), immunotoxicology (Team2) and the microbiome involvement in liver disease (Team3).

The scientific programs are focused on providing mechanistic insights, at the molecular level (e.g., on low molecular weight chemicals, Team2) and using molecular, cellular, in vitro (e.g., 3D culture systems [Team1], human biopsies [Team3]) and in vivo (animal facility with up to 3500 mice) models and clinical populations (e.g., as part of the Micmaf cohort of patients with alcoholic liver disease [ALD], Team3).

Weaknesses and risks linked to the context

The link between the scientific programs of the three teams (viral persistence <-> immunotoxicology <-> liver disease) is not obvious and degree of collaboration between the teams not entirely clear. The scientific objectives include areas that would seem suitable for more collaborations, which are not clearly outlined and may not have been established. For example, Team3 support for virome analysis of Team1; investigation of gut

microbiome context by Team3 of symptomatic/pathological HPV infection for Team1 or of allergic and inflammatory responses for Team2.

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 comprises a multidisciplinary (immunology, virology, cell biology) academic and clinical (from several hospitals, including Paris-Saclay) research team. The unit has trained and mentored 31 PhD students (27 defended their PhD for 20 HDR) and 68 graduate students including nineteen Master 1, 47 Master 2 and two Erasmus students within an international context. The unit involves 65 people comprising 25 permanent research staff scientists, which are relatively evenly distributed across the three teams (8-9 permanent research staff scientists, 7-10 PhD and MSc students).

The unit is associated with two graduate schools (HeaDS and LSH) and contributes to the large, multidisciplinary Healthi Interdisciplinary Program (led by Team2's leader) with 136 teams. It is also steering two large, multidisciplinary projects, including the Structure Fédérative de Recherche Institut Paris-Saclay d'Innovation Thérapeutique (Ipsit-SFR, Dir. Team 1 head), which includes 28 teams (11 laboratories) and a service unit (Ipsit-UMS Inserm-US31 CNRS-UMS 3679), which comprises eleven technical platforms.

The unit has established state-of-the-art technology, including an experimental histology platform attached to the Ipsit-UMS and CyTOF/Helios mass cytometers (as part of the FlowCyTech project), as well as Meso Scale Discovery technology platforms (QuickPlex® SQ 120) for multiplexed measurement of molecules in biological samples (CYM PF), Light- sheet fluorescence microscopy for the analysis of clarified tissues (PHI PF) and equipment for metabolic assays (Seahorse real-time metabolic).

The unit's budget (in average 27%, excluding salaries of permanent staff) is provided by institutional funding from Inserm and UPSaclay. The rest comes from external sources: grants from national agencies (ANR (8); Anses (2); Inserm (1)); GS and OI (8); PIA (3); EU (3), private foundations (including FRM (2); SNFGE (2); Afef (2)); Biocodex (1); industrial partners (including Servier, Pierre Fabre, Inderm, Solvay, Idorsia, Bayer Crops Science, Stallergenes, X4-Pharmaceuticals, Bioprox) and SATT (4).

The financial resources of the unit show a positive trend towards increased recurrent fundings and external resources.

Weaknesses and risks linked to the context

So far, access to more advanced sequencing technologies (e.g. whole-genome shotgun sequencing, RNA-seq, lipidomics) has been limited and reliant on shared resources at Paris-Saclay or external services. Bioinformatics support is only provided through training of team members, plans for recruitment of bioinformatics Master's students at Paris-Saclay and the UMS Ipsit bioinformatics platform, but trained bioinformatics are not part of the team.

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

Laboratory life of the unit is regularly discussed with the head of the unit, team leaders and the unit's administrative staff manager. Moreover, different meetings are organized as general assembly, meetings with researchers or with the staff of the joint service support in addition to the annual career development meeting. Each team leaders have the opportunity to meet regularly the technical staff.
The unit has elaborated an evolutive document laboratory containing rules of procedure and charters.
Several promotions (5) have been obtained for the technical staff during the last mandate. The unit has health and safety officers and is committed to training new arrivals and preventing psycho-social risks. It is sensitive to the exposure of pregnant and maternity women, and is committed to the integration of people with disabilities. It has taken gender parity into consideration and the proportion of women at leadership position is improving. The unit complies with the rules of ethics, open science and scientific integrity notably for animal

experimentation and human samples and cohorts use. Data protection and sharing is under the responsibility of the Direction des systèmes d'informations of Saclay university and guaranties appropriate data traceability. Endly, the unit has identified a resource person to work on the prevention of environmental risks and sustainable development. Compliance with health and safety practices, gender equality, scientific integrity and ethics, protection of scientific assets and computer systems, and environmental risks and sustainable development objectives is appropriate.

Weaknesses and risks linked to the context

Communication is uneven when it comes to disseminating general information about the laboratory's members. The main areas for improving communication are to ensure consistent sharing of information between teams, with team leaders responsible for ensuring equal access to organizational updates.
Technical skills and expertise should be shared to standardize experimental practices and increase efficiency. The establishment of a laboratory council, meeting three times a year, with representatives of researchers, technicians, administrative staff, doctoral students and post-doctoral fellows, must be updated in order to facilitate discussions on the laboratory's organization and scientific direction. All scientific presentations are not held in English, and language courses in English or French should be encouraged to improve communications with international colleagues.

EVALUATION AREA 2: ATTRACTIVENESS

Assessment on the attractiveness of the unit

The assessment of the unit's attractiveness is excellent, highlighted by the recruitment of a PU Inserm Chair, prestigious recognitions such as participation in two ITN collaborations, two "Equipe FRM" labels, and competitive national funding (with 5 out of 9 ANR grants led by the unit). However, the limited number of permanent Inserm scientists and a reliance on temporary technical contracts present moderate risks for project continuity. Additionally, while the unit is well-equipped with advanced facilities, its dependency on shared platforms may affect access and technological competitiveness if external policies or funding constraints shift.

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

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

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

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

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

The unit has collaborated in two Marie Sklodowska-Curie Innovative Training Networks, with the most recent set to conclude this year. The award of the prestigious "Equipe FRM" (2017-2020 and 2022-2025) label to two of its teams highlights its recognition by international scientific juries. The unit's attractiveness is further enhanced by its recruitment strategy, as evidenced by the successful hiring of prominent researchers (one PU in Cellular and Molecular Immunology and one PU Inserm Chair), as well as technical staff with diverse expertise. Additionally, there has been a substantial number of PhD students enrolled in the unit, with a total of 27 PhD students, of which 14 are still under contract.

Additionally, the unit has achieved significant success in securing competitive funding, primarily through national contracts such as those from ANR and Anses, where it often serves as the leading partner (8/10). It has also obtained contracts funded under the PIA, with approximately half of these awarded to the unit as leaders. Furthermore, the unit has developed strong partnerships with socio-economic and cultural entities, including collaborations with industry and SATT, which enhance its funding capabilities. It has also received financial support from charitable organisations and foundations, such as SNFGE, FMR, and Afef, all of which contribute to its research initiatives. The presence of major equipment and technical facilities, such as the newly approved

animal facility at the Henri Moissan Faculty of Pharmacy, provides cutting-edge infrastructure that is highly appealing for advanced research and training.

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

The unit's broad range of research areas, while fostering interdisciplinary work, may dilute a cohesive research identity, potentially limiting its visibility and distinctiveness in the European Research Area. This lack of thematic focus could hinder its competitive positioning and recognition, affecting its ability to attract international collaborators and secure European funding. The limited number of full-time Inserm scientists further poses challenges for project continuity, especially as senior researchers retire. Additionally, the unit relies heavily on temporary contracts to fill technical roles, with eight engineers and technicians recruited on short-term contracts between 2018 and 2023, often due to constraints on securing recurring funding. This reliance on temporary staffing threatens the continuity of technical support, risking project stability if skilled personnel leave. Lastly, while the unit is well-equipped, with recent investments in specialised platforms like the Meso Scale Discovery technology, maintaining and upgrading this equipment requires continuous funding. The unit depends on shared platforms provided by the Structure Fédérative de Recherche Institut Paris-Saclay d'Innovation Thérapeutique, which, if access policies or budgets shift, could limit the unit's access to essential resources. This dependency, combined with the potential constraints on emergency funds for equipment renewal, may affect the unit's technological competitiveness in the long term.

EVALUATION AREA 3: SCIENTIFIC PRODUCTION

Assessment on the scientific production of the unit

The scientific production of the unit is very good. The unit published 49 original articles as primary investigator in both multi-disciplinary and specialty journals, including notable publications in *Nature Communications*, *PNAS*, *Cell Reports*, *Blood*, *Science Translation Medicine* and *Gut*. Author positions in publications is appropriate, in particular PhD students being first authors. There is considerable heterogeneity in the scientific production between teams, with Team 1 having an excellent output while the scientific production of Team 2 and 3 is less visible.

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 teams' scientific production is proportionate to the number of PIs and personnel. In the 2018-2023 period, Team 1 has published twelve original articles, Team 2, 25 original articles and Team 3, twelve original articles (only including lead or last authorship for PIs, excluding collaborations and reviews).
Major achievements include publications as lead or last authorship in high-profile generalist and specialty journals: *Nat Comm* 2020, *Blood* 2021, *Cell Reports* 2022 for Team 1; *Allergy* 2018, *Allergy* 2019, *Sci Transl Med* 2019 for Team 2; *Gut* 2021 and *JHEP Reports* 2021 for Team 3.

Scientific highlights include for Team 1 the characterization of patients with biallelic mutations in CXCR2 (Hematologica 2022), the discovery of altered activation state of DC subsets and tissue inflammation in mice expressing a WHIM syndrome-associated CXCR4 mutant (Blood 2021), the treatment of skin lesions associated with autoimmune and inflammatory diseases using the As2o5 arsenic compound (European Patent EP3766505); for Team 2 the description of new mechanism of neuromuscular blocking agents (NMBA)-induced anaphylaxis, related to neutrophil and platelets activation by specific IgG immune complexes (Sci Transl Med 2019), the discovery that Nrf2 regulates neutrophil recruitment and accumulation in skin during contact hypersensitivity (J Immunol 2019), the identification of T-cell epitopes from benzylpenicillin conjugated to human serum albumin (Allergy 2018); for Team 3 the demonstration that liver lesions in mice transplanted with human stools from an

alcoholic patient can be abrogated by a pectin treatment through the AhR pathway (Gut 2021) and that pectin also acts through bile acid modifications that are independent on the TGR5 receptor (JHEP Reports 2021). Authorship seems appropriately shared. PhD students consistently publish first author papers in all 3 teams. The scientific production of the unit complies with the principles of research integrity and ethics. Means to implement traceability and reproducibility are appropriate (laboratory notebooks). All research from the unit is in line with ethical guidelines from governing bodies. The unit shows commitment to transparency and open science as demonstrated by the publication of pre-prints (1 in medXriv and 2 in bioXriv).

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

The unit has numerous publications (only including lead or last authorship for PIs, original articles and reviews) in journals that are considered of low quality by governing bodies including Inserm, i.e. journals with high acceptance rate and limited peer-reviewing (in particular of the MDPI group and Frontiers journals). For Team 1 (23% of their publications): Front Cell Infect Microbiol. 2023; Front Immunol. 2022; Int J Mol Sci. 2022; Cancers 2022; Viruses 2021; Cells 2021 (x2); Front Immunol. 2018. For Team 2 (19% of their publications): Front Immunol 2023; Front Toxicol 2023; Viruses 2023; Antioxidants 2023; Front Immunol 2022; Cells 2022; Antioxidants 2022; Front Toxicol 2022 (x2); Front Immunol 2021; Nanomaterials 2020; Front Immunol 2020; Front Immunol 2019 (x4). For Team 3 (15% of their publications): Nutrients. 2022; Cells 2022; Nutrients 2021. The publication strategy of the unit is unclear. There is heterogeneity between teams, in particular in terms of volume versus quality of publications.

EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

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

The inclusion of the unit's research in society is excellent. Fourteen private projects were performed with seven Cifre grants. The members of the unit are involved in clinical trials with cohorts. They filled three international patents and the creation of a start up is in process. The unit is involved in public outreach to share scientific results with books, radio, TV interventions and host of high school students.

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 continuously searched for applications of their research. Hence, teams have established collaborations with chemical, pharmaceutical and biotechnology companies with numerous research contract (14 projects) in the context of partnership with Servier (teams 2 and 3), Solvay (team 2), Pierre Fabre (team 2), Bayer Crops Science (team 2), Thor (team 2), X4-Pharmaceuticals (team 1), Idorsia Pharmaceuticals Ltd (Team 1), ProbioSwiss SA (team 3) and Bioprox (team 3). This partnership was often supported by PhD grants (Cifre). The units have established seven PhD Cifre contracts during the last five years. The unite due to its translational research has long term collaborations with clinical sector in several regional hospitals (Ambroise-Paré, Kremlin Bicêtre, Antoine Béclère, Bichat-Claude Bernard, Paul Brousse and the Paris-Saclay hosp) and participate to the FHUs Hepatinov, Care and the IHU Prometheus (2023). This research was also supported by clinical research contracts (Local call: CRC Endophen, Covall – National call: PHRC Mesynad). Their research is also based on cohort monitoring (Abirisk…) and clinical trials (management of IM by fibbers in patients with alcohol disorder, Team 3). The Unit search for technical transfer opportunities with the SATT Paris Saclay (Team 1: a tech transfer program in 2018-2020 – a Call Poc in Labs in 2020 and a PhD transfer program in 2023 – Team 2: a Call Poc in Labs - Team 3: a maturation project in 2020). The unit is attentive to fill for patents where possible; several patents were registered (two European patent and a US patent) with the development of a universal skin model, the development of humanising the skin-immune system in mice as a preclinical model, the treatment of skin lesions associated with autoimmune and inflammatory diseases. A patent was filed for method and pharmaceutical composition for use in the treatment of nutritional diseases or metabolic syndrome. Team 2 participated to the validation program of a new human anti-adalimumab antibody organized by the NIBSC (National Institute for

Biological Standards and Control) under the frame of WHO. A start-up company is in the process of being created for the development of a topical drug for the treatment of skin lesions associated with lupus. Concerning interaction with public and society, the unit participate to "les nuits de la lecture U. Paris Saclay", the public lectures in media library, the redaction of books for students (in particular team 2 and 3). Finally, members of the unit also regularly speak on various media including television channels (mainly team 3 for France5, France 2), radios (RTL, Europe 1…) and press (le Quotidien du médecin, 60 millions de consommateurs), interventions within associations or via the creation of blog on website. The unit have a long-standing policy of welcoming middle and high school students into the unit.

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

The unit have developed collaborations with the private sector sharing scientific questions, the unit must be attentive to maintain their scientific autonomy.

ANALYSIS OF THE UNIT'S TRAJECTORY

A change in leadership is proposed for each Team as well as for the Unit. The proposed transition to the next generation is based on experienced researchers with a track record of publications, awards and collaborations within the unit. G. Schlecht-Louf, S. Kerdine-Römer and A.M. Cassard have a history of collaborations within the unit (e.g. two grants from the Labex LERMIT in 2018 and ANR in 2022) and joint publications (e.g. on studying chronic skin inflammation in 3D-epithelial cell cultures). This proposal is convincing to maintain continuity in the research projects and Unit organisation.

G. Schlecht-Louf (Team1) has been working with the team since 2011, as full professor since 2020, and served as a co-leader of two Master's programs, scientific advisor for Ipsit-SFR and Ipsit-UMS Inserm-US31 CNRS-UMS 3679, and collaborator of large research projects (e.g., the Marie Sklodowska-Curie Actions training network ONCOgenic Receptor Network of Excellence and Training 2.0) and industrial partnerships (e.g., the X4 Pharmaceuticals (US/Austria) -Dissecting the biology of HPV infection with regards to the CXCR4 axis and WHIM). S. Kerdine-Römer (Team2), full professor since 2011, had already been leading one of the Team2 axes (Nrf-2 role in skin immunopathology), is head of the pharmacology/toxicology section of the doctoral school "Innovation Thérapeutique du Fondamental à l'Appliqué" (ED569) and has been scientific advisor for the Actagen platform (Ipsit-UMS Inserm-US31 CNRS-UMS 3679). She has received continuous research and industrial fundings. A.M. Cassard (Team3), DR since 2018, already co-headed Team3 with G. Perlemuter during the last period and will now also serve as director of the unit. She has an impressive track record including research funding from ANR, Inserm, or IRIS.

The unit will focus on investigating the "impact of environmental players on the immune and inflammatory processes of biological barriers in the context of disease", continuing a successful and relevant research trajectory that is broad enough to encompass the different research areas of Team1-3 while allowing for expansion and innovation. For Team1 the expansion of research on HPV from pathogenic to commensal mechanisms and broader 'virome' communities, using both newly established 3D-epithelial cell culture and planned organoid systems, is convincing and promising. For Team 2, planned projects and applied technologies are in line with previous work and the links to projects of Team1 and Team 3 are less clear, although the research on therapeutic proteins and nano-objects and their aggregates seems relevant (e.g. with clinically used anti-TNF antibodies). Team3 convincingly expands microbiome research in the broader context of metabolic liver diseases with mechanistic (e.g., on mucosal immunology with Team1 or postprandial lipidomic analyses) and clinical projects (e.g., using the French Micmaf cohort, the filed patent for protective bacteria, or fecal microbiota transplantation preclinical models), using advanced new technologies (e.g. liver-on-a-chip, gnotobiotic rodent models).

RECOMMENDATIONS TO THE UNIT

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

In terms of communication, several points have been highlighted that could be improved. There is a heterogeneity in the transfer of general information concerning the organization of the lab, which does not equally involve all team members. Team leaders should ensure that the communication within their team and with other teams is clear and give the same level of information to each lab member as disparities between teams are noticed. Similarly, the allocation of resources between and within teams should be fully transparent. The teams of the unit should also share technical and lab expertises to harmonize experimental practices and increase efficiency. As per Inserm rules, the unit is required to form a lab council that should meet a minimum of three times per year with representatives of all category of personnel (researchers, technicians, administrative staff, PhD students and post-doctoral fellows) to discuss the lab organization and scientific orientation of the unit.
Scientific presentations during weekly unit meetings should always involve English text and should be held in English whenever possible to better integrate foreign team members. Intensive English or French courses, as required, should be encouraged to facilitate exchanges with foreigners.
A green lab committee should be established to address environmental concerns and make recommendations to reduce the environmental footprint of the unit and improve its sustainability.

Recommendations regarding the Evaluation Area 2: Attractiveness

To enhance the unit's attractiveness, increasing international visibility and recruitment is essential. Advertising post-doctoral positions on global platforms such as *Nature Jobs* as well as social media such as LinkedIn could attract high-quality candidates, particularly from abroad, and conducting meetings and seminars in English would create a more inclusive environment for international researchers. Offering both French and English language classes would further support the integration of foreign fellows. Additionally, securing permanent positions through targeted programs like *ATIP-Avenir* and *FRM Amorçage Jeune Équipe* could strengthen the core team, especially with the advantage of the new facilities. Finally, fostering inter-team collaborations, such as joint projects on microbiome analysis between Team 1 and Team 3, and pursuing joint funding applications would increase interdisciplinary research impact and improve resource sharing within the unit.

Recommendations regarding Evaluation Area 3: Scientific Production

Recommendations are to increase the visibility of their work by targeting multidisciplinary journals with a broad audience.

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

In terms of contribution of research activities to society, the recommendations aim to maintain a balance between fundamental, translational, and technological research to favor an environment for innovation; to continue to be attentive to the technological transfer opportunities by filling patents when it is appropriate.
For expertises in national and international institutions (essential for the transfer of knowledge to the public policy actors), the recommendation is to maintain a reasonable balance between all the activities of some members of the unit (teaching, research, expertise …). A recommendation could be done to coordinate actions dedicated to the public by developing a strategy of the unit for the participation to "fête de la science" or for the short observation internship for collegians and high school students as already done.

RESPONSES TO SUPERVISING BODIES CONCERNS (IF ANY)

NA

TEAM-BY-TEAM OR THEME ASSESSMENT

Team 1: Immunoregulation, Chemokines and Viral persistence

Name of the supervisor: Ms Françoise Bachelerie

THEMES OF THE TEAM

The main theme of Team 1 is the investigation of immune disorders and infectious diseases associated with Human papillomaviruses (HPVs), including cancers and severe skin lesions. Team 1's goal is to understand the interplay between immune cells and the skin microenvironment, focusing on key regulators, in particular the chemokine CXCL12 and its receptors CXCR4 and Atypical Chemokine Receptor 3 (ACKR3), the glucocorticoid-induced leucine zipper (GILZ) and calcium channels.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

One main recommendation was to strengthen valorisation and outreach. Team 1 has been investing in technological development and pursuing several translational projects. In particular, Team1 was awarded Technology Transfer grants for the "Treatment of skin lesions associated with autoimmune and inflammatory diseases by arsenic salts" (2018-20), to develop a pilot study on humanising the skin-immune system in mice as a preclinical model (2020) and a PhD fellowship was obtained (Dec. 2023-2024). Team1 is also in charge of managing a pillar dedicated to innovation in technological development for health in the "IHU Prometheus", a 10-year project awarded in 2023. Overall, Team 1 has adequately addressed this recommendation.
Another recommendation was to increase the international visibility of the team. In the 2018-2023 contract, four out of nine PhD students were foreigners, as well as all recruited postdocs. In addition, Team1 was awarded one Inserm Chair award and recruited Julien Pothlichet in 2023 as a result of an international competition. Moreover, Team 1 has participated as collaborator in two European program Marie Skłodowska-Curie Action Innovative Training Networks (ITN), Oncornet (2015-2019) and Oncornet2 (2020-2024), in which three PhD students from Spain and the Netherlands were supervised.
The team has also developed several original mouse models with which they have established international long-term collaborations on neutrophil biology with Lai Guan Ng (Singapore) and on papillomavirus/host interactions with Paul Lambert (Madison, Wisconsin, US). Team 1 had a central role in establishing an international research network (iGPCRNet) founded in 2021 that includes German and UK teams as well as a Chinese laboratory from Huazhong University (Wuhan, Hubei) and in organising the first iGPCRNet meeting in 2021.All of this shows that Team 1 has obtained significant international visibility.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2023

Catégories de personnel	Effectifs
Professeurs et assimilés	2
Maîtres de conférences et assimilés	4
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	**10**
Enseignants-chercheurs et chercheurs non permanents et assimilés	1
Personnels d'appui non permanents	1
Post-doctorants	2
Doctorants	3
Sous-total personnels non permanents en activité	**7**
Total personnels	**17**

EVALUATION

Overall assessment of the team

Scientific production: excellent. The team has made significant discoveries in the field, which are published in high visibility journals (both multidisciplinary and specialty journals), such as Nat Comm, PNAS, Cell Reports, Blood.
Attractiveness: excellent. The team has attracted major funding, including competitive national grants (2 ANR grants as coordinator, FRM labelled team) and European collaborative grants (Infect-Era, ITN network).
Valorisation: excellent. The team has filled three patents and a start-up company is being created. The team has obtained industrial funding for translational research (3 grants).
The overall assessment of the team is excellent.

Strengths and possibilities linked to the context

A major strength of Team 1 is their strong expertise in an important yet understudied theme, and the development of original in vivo and in vitro models to study the biology of HPV, as well as ex vivo use of human clinical samples.
This recognised expertise has created opportunities for engagement in European collaborative projects such as the Infect-Era on *Human Papillomavirus infection: from molecules to tissues to prevention*, which was coordinated by Team 1 (2016-19), and participation in the multidisciplinary consortium of ITN network Oncornet2.0. It also laid the foundations for fruitful collaborations with international laboratories, leading to high visibility publications not in lead position (Nat Immunol 2019, Nat Comm 2022, Immunity 2018, Immunity 2019, Nat Med 2019).

Team 1 has performed very well in obtaining diverse funding as PIs to support its research program, through national calls (ANR Ochre 2020-24 , ANR Osteovalymph 2018-20, Fondation Recherche Medicale Label Équipe 2022-25, Ceredih Centre de référence des déficits immunitaires héréditaires 2020-21, Association Laurette Fugain 2017-18), and has obtained industrial partnerships (X4 Pharmaceuticals, Idorsia Pharmaceuticals) and funding for translational research (Tech Transfer Program Satt Paris-Saclay 2018-2021).
Valorisation output is excellent (3 patents and creation of a start-up company).
PIs from Team 1 have had numerous invitations to speak at conferences (mostly national and a few international), which is very satisfactory in the context of Covid pandemics and demonstrates the excellent scientific reputation gained by the team.
Scientific production is excellent with very regular publications and some articles in lead or last authorship with high visibility in prestigious generalist journals (Nat Comm 2020, PNAS 2023, Cell Reports 2022) as well as high profile specialty journal (Blood 2021).

Weaknesses and risks linked to the context

Some of the support research staff, especially permanent positions, will be leaving or is been dedicated to collective missions. It is surprising that Team 1 does not have any funding from cancer-specific charities for the HPV tumour-related projects. Some of the projects were delayed because of the lab moving to the Orsay campus. Although the team has implemented a contingency plan, special attention should be paid to these projects to ensure their completion. Another weakness is that PIs of the team are not in lead/last position in the most visible scientific publications which result from collaborations. Finally, collaborations with other teams of the Unit seem limited.

Analysis of the team's trajectory

Recruitments of three new project leaders increase the team's workforce and expertise, supporting the development of their research program: one Professor UPSaclay joined Team1 in early 2019; one Assistant Professor UPSaclay joined Team1 in September 2021; one Inserm Scientist was recruited in 2023 within the framework of the Inserm Chair award and joined Team1 in February 2024. These new project leaders all have obtained funding for their projects.
An Assistant Professor in Immunology will be recruited in September 2024. An assistant hospital-university will be recruited in September 2024. The team dynamics is therefore very positive.
The proposed scientific project aims to better understand the functioning of HPV virome, to increase our knowledge of the relationship between HPV virome composition and immune fitness and disease development. The team will also pursue their long-term project of generating a novel model of epithelium hosting a cHPV virome. This is an ambitious and innovative project, and the team is very well positioned to make significant breakthroughs.

In addition, a start-up company is in the process of being created for the development of a topical drug for the treatment of skin lesions associated with lupus.
In conclusion, the team is on a very favourable trajectory with promising scientific projects.

RECOMMENDATIONS TO THE TEAM

Team 1 members should increase their collaborations with other teams of the Unit, which would be beneficial for both their own projects and the other teams.
Because Team 1 has a lot of different PIs with diverse projects, another recommendation is to better integrate the projects of P. Bobé into the Team, and to hold regular meetings with all PIs to discuss scientific orientations and collective strategy for funding.

Team 2: Drug and Chemical Allergy, Immunotoxicology and Immunopathology

Name of the supervisor: Mr. Marc Pallardy

THEMES OF THE TEAM

Team 2 is addressing the mechanisms of immunisation to LMWC (low molecular weight chemicals), environmental allergens and therapeutic proteins in the context of allergic and inflammatory diseases, with a specific emphasis on skin allergy.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Regarding publications in higher profile journals, the team has published articles highlighting the technological and clinical aspects as recommended in the previous evaluation reports however some publications are still in low impact journal.
The research strategy of the team is mainly focused on fundamental research however the team has followed the recommendation of patent or technology transfer and worked for it when adapted. The team had recently obtained a Patent-SATT- Poc-Lab grand from the SATT Paris-Saclay and participated to the validation program of a new human anti-adalimumab antibody organised by the NIBSC (National Institute for Biological Standards and Control) under the frame of WHO.

Concerning the strategy to attract a full-time researcher and long-term post docs, it must be noticed the effort of the team to obtain a teaching discharge for a professor, to recruit two new assistant professors and to identify a permanent full researcher (even if it was not successful). A recent success in a PEPR project will allow the recruitment of a non-permanent full scientist as a post doc. It is important to notice that the last few years, the conditions were not the most attractive with the moving from Chatenay-Malabry to Saclay site and the Covid period.

The team has developed its research with clearly defined priorities with three axes managed by PIs who successfully obtained different grants (Anses, ANR, PEPR). They have performed continuous effort to respond to the ANR calls and to EU program Marie Skłodowska-Curie Action Innovative Training Networks (ITN) with no success to the last call. However, all this work resulted in the constitution of an informal European network and an increasing visibility of the team with European partners.
Team 2 has maintained various collaborations with pharmaceutical, chemical and cosmetics companies mainly through scientific co-constructed research activities with the recruitment of PhD student (Cifre fellowships) and consistent with their research questions.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2023

Catégories de personnel	Effectifs
Professeurs et assimilés	3
Maîtres de conférences et assimilés	5
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	3
Sous-total personnels permanents en activité	**11**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	0
Post-doctorants	0
Doctorants	8
Sous-total personnels non permanents en activité	**8**
Total personnels	**19**

EVALUATION

Overall assessment of the team

The scientific production is very good with regular publications in specialty journals, related to clinical investigations as PI for half of them, some in high-profile journals related to allergy (J of Allergy) and clinical immunology, and to toxicology research mainly as PI (Part Fibre Toxicol 2023, Toxicology in vitro 2020).

The team's attractiveness is very good as attested by its ability to raise funds at national grant as PIs through national call PNREST-Anses (Immuquap- Allergosil) and as partner in the PEPR-ANR Accredia. Team 2 has important clinical outreach, partner in the FHU Care and the IHU Prometheus and in obtaining clinical funding (as PIs 2018-23 Endophen- 2021-2022 Covall or as partner PHRC Mesynad). Members of the team are involved in international (WHO, IARC) and national expertises (Anses, ANSM, INRS).

Valorisation is excellent with thirteen industrial collaborations (6 Cifre) and participation to the validation program of a new human anti-adalimumab antibody organised by the NIBSC (National Institute for Biological Standards and Control) under the frame of WHO.

Strengths and possibilities linked to the context

Team 2 have a long-term recognised research activity in the understanding of physio pathological mechanisms of immune inflammation mainly focused on the role of dendritic cells and neutrophils with the comprehension of the skin microenvironment in the mechanism to allergic contact dermatitis and cross talk with Ntf2), the comprehension of mechanisms of immunisation to low molecular weight molecules, nanoparticles, therapeutic antibodies with the emergence of questions on how aggregated-therapeutic antibodies trigger an adaptative immune response against therapeutic antibodies, and the identification of new roles for PMNs in allergy and Sars-CoV2 infection. A major strength of Team 2 is to conduct research from genes to human samples and cohort (Abirisk, Egea…), essential to have a global approach on allergy. To study the skin microenvironment, they used different models such as the KC 3D model developed by team1. Their research aims to propose a predictive approach for allergy disorders in patients. A strong link between fundamental research and clinically relevant outcomes leads them to be involved in the FHU Care and the IHU Prometheus (team 1 and team 2 collaboration) and obtaining clinical founding (as PIs 2018-23 Endophen, 70kEuros) or partner (CovallL, 20kE, 2021-2022 and PHRC Mesynad, 2023-2027, 10kEuros).
Two young assistant professors were recruited (2018-2023) reinforcing the competence on cell biology of the team.
Members were involved in interdisciplinary projects as founding members of the Labex Lermit and its continuation through Healthi program. This was an opportunity to develop research with team 3 (effect of xenobiotics exposure on the AhR pathways activation by bacterial indoles in ALD). The team performed very well in obtaining other diverse research programs as PIs through national call PNREST-Anses (IMMUQUAP-Allergosil, 70kEuros) and as partner in the PEPR-ANR Accredia (development of innovative antibodies, 213kEuros). They have performed continuous effort to respond to the ANR calls and to EU program Marie Skłodowska-Curie Action Innovative Training Networks (ITN) with no success. However, all this work resulted in the constitution of an informal European network and an increasing visibility of the team with European partners.
Team 2 had historical industrial collaborations and developed more recently partnerships with Servier, Solvay or Inderm sharing scientific question on immunogenicity and inflammatory process concerning therapeutic proteins, nanoparticles, or light exposition and the grants for PhD students (6 Cifre). The team had participated to the validation program of a new human anti-adalimumab antibody organised by the NIBSC (National Institute for Biological Standards and Control) under the frame of WHO. Members are recognised for their expertise in allergy field and participated actively to public expertise through committee at national (ANSM, Anses) and international levels (IARC, WHO). Their expertise serves subjects with health issues (bisphenol A, PFOA- co-author of an article in Lancet Oncol). Members of the team are involved in the EU Program PARC of assessment of risks for chemicals.
The responsibility of the team in doctoral (pôle Pharmacologie-Toxicologie de l'École Doctorale Innovation Thérapeutique: du Fondamental à l'Appliqué (Itfa), Université Paris-Saclay) and master (Therv, Toxicologie Humaine Evaluation des Risques, Vigilance) formation linking teaching and research is favourable for the recruitment of high-level master (21 master 2) and PhD students (19). Eleven thesis were defended, eight thesis are in progress for five HDR.
PIs from Team 2 have had numerous invitations to speak at conferences (16 nationals, 23 internationals). The scientific production has regular publications in specialty journals, related to clinical investigations as PI for half of them, some in high-profile journals related to allergy (J of Allergy) and clinical immunology, and to toxicology research mainly as PI (Part Fibre Toxicol 2023, Toxicology in vitro 2020).

Weaknesses and risks linked to the context

Some works are published in MDPI group journals (4/90 publications from 2018 to 2023).The huge implication of members of the team in teaching and in the direction of master and doctoral formation is at risk for research. The absence of full-time permanent researcher and international post-doc remains a key question to optimize the development of the team research activities. The departure of clinicians from the team could slow down the translational research activities. The difficulty to success to European calls could ultimately weaken their position as a leading team in the field of immunotoxicology in Europe.

Analysis of the team's trajectory

The new team leader has showed her capacity to develop research project as leader of research on the role of the transcription factor Nrf2 in immunotoxic reactions induced by chemical molecules since her nomination as professor in 2011 in the unit. Her involvement as scientific co-leader of the plateforme de Transcriptomique et Protéomique (Actagen), de l'Institut Paris-Saclay testifies her capacity to manage collective research activities. She demonstrated her ability to coordinate team activities as leader of the "pôle Pharmacologie-Toxicologie de l'École Doctorale Innovation Thérapeutique: du Fondamental à l'Appliqué (Itfa), Université Paris-Saclay".

Team 2 has a long-term recognised research activity in the understanding of physio pathological mechanisms of immune inflammation due to allergens exposure (nickel, nanoparticles, beta lactams and biopharmaceutical products) mainly on the role of dendritic cells and neutrophils. With the moving of two "bi-appartenants" clinicians, the research project naturally was focused on the mechanisms of skin allergy and the role of Nrf2 by studying immunometabolism and on how therapeutic proteins or nanoparticles trigger an adaptive immune response into the continuation of work undertaken. This ambitious scientific project shares major health questions related to immunoallergic processes and exposition to nanoparticles or to bioPharmaceuticals products. With the increase in the incidence of skin allergies and the increase of biomolecules for treatment, improving knowledge on the one hand of the chemical substances concerned and on the other hand on how these substances trigger a response on immune system is essential.
The project aims to explore new technological approach with "omics" in order to provide new biomarkers and explore the dialogue between cells and cells activation.
The project is already supported by the PEPR Accredia awarded in 2023 and the recruitment of a full permanent researcher with a post doc who will reinforce the research capacity of the team. This project will benefit from the clinical environment through the FHU Care and the IHU Prometheus (team participate to the steering committee).
This project also relies on the partnerships built with industrial partners i.e. Solvay (silica nanoparticles) and Servier (Immunogénécité des protéines théraeutiques), three grants for PhD students are running.
Through the Abirisk consortium, PARC program and international expertise, the team is recognised at the international level which is an asset for the project and for future European call.

RECOMMENDATIONS TO THE TEAM

Despite the future recruitment of a post doc, the team should maintain attractiveness politics to recruit permanent researcher. Team 2 should better define the collaborations within the unit with researchers with complementary expertise (team 1 for 3D model). Team 2 should maintain their efforts to respond as PIs at national and European calls to reinforce the attractiveness of the team and maintain the team as a leader in Europe in immunotoxicology research. Team 2 should sustain their young assistant professor to respond to ANR JCJC and to take HDRs as soon as they meet the conditions.
Members should maintain, if possible, the teaching discharge and be attentive to the balance between pedagogical investment in master and doctoral formation and research activities particularly for the two young assistant professors. They should maintain when appropriate their efforts to transfer technology and to file patents. The experimented researchers are involved in many structures of research management at UP Saclay and in national and international expertise structures. The leader should be aware of maintaining the best balance between all these activities.

Team 3: Microbiome in liver disease: from susceptibility to treatment

Name of the supervisor: G. Perlemuter & A.-M. Cassard

THEMES OF THE TEAM

The team investigates the physiopathology of liver diseases, specifically alcoholic liver disease. They focus on the metagenomic characterisation of the intestinal microbiota and its role in disease susceptibility and liver homeostasis. Their work includes studying bacterial diversity, host defense mechanisms, and the impact of microbiota-derived metabolites on liver and gut health.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

It is clear that the research team has taken the Hceres committee's recommendations into consideration and has made efforts to address them, although some objectives have not been fully achieved. Regarding publications in higher-impact journals and valorisation of work on intestinal microbiota, the previous 2018 evaluation recommended publishing in multidisciplinary journals. The team has attempted to publish in higher-impact journals but has often been redirected to specialised journals by the editors. Nonetheless, two articles were published in Scientific Reports. A team 3 member coauthored a Nat. Rev. Micr. article. Notable efforts have been made to meet this recommendation, although the results are mixed. A recommendation was made to increase valorisation. The team received support from SATT Paris-Saclay for a maturation project and filed a patent in January 2024. This recommendation has been followed and successfully implemented, although the patent must be approved and the ability to commercialize findings demonstrated.

In terms of attracting full-time scientists and long-term post-docs/highly qualified technicians, the team secured an FRM contract for a post-doctoral researcher, but the candidate could not establish herself on the project. Efforts were made to recruit a researcher from the Weizmann Institute, but she ultimately obtained a position elsewhere. Despite efforts to attract talent, this recommendation remains a weakness. Concerning the definition of scientific priorities, the team has taken steps to attract researchers (PUPH, MCU-PH, and an engineer). The measures taken demonstrate an awareness of scientific priorities, although the lack of full-time researchers remains an issue.

Regarding securing funding and initiating new collaborations, the team has obtained ANR fundings. Despite some failures, there are continuous efforts to secure funding. In terms of organisation to interact with the clinical department at Saclay, the team has anticipated the reorganisation with the opening of Paris-Saclay hospital and has already integrated doctors from Longjumeau hospital. The implementation of an effective organisation to interact with the clinical department seems well underway.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2023

Catégories de personnel	Effectifs
Professeurs et assimilés	1
Maîtres de conférences et assimilés	2
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	**6**
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	**11**

EVALUATION

Overall assessment of the team

The scientific production of the team is very good. Publications in large audience journals remain limited.
The team's attractiveness is very good, demonstrated by success in securing competitive grants such as two ANR projects, a FRM Team Label, and an Inserm Transversal Program. Team members also serve as reviewers of international grants and committees, despite a lack of permanent researchers, technical personnel and post-doc fellows
The team has shown excellent valorisation, with achievements that include industrial partnerships (IRIS), two Cifre-Servier agreements, a patent filing supported by SATT, and involvement in patient cohorts and clinical trials, particularly for fibre treatment in alcohol use disorders.

Strengths and possibilities linked to the context

Under the joint leadership of a scientific researcher and a clinician-researcher renowned in gastroenterology and nutrition, the team has cultivated robust interdisciplinary collaboration between clinical and basic research domains (e.g., Transversal Program on microbiota Inserm (216k€) by team leaders and two ANR - CE17, 223 kE). Target the gut microbiota by prebiotics to improve ALD progression, CE18, Timpah (244K€/582k€) by AM. Cassard). This collaborative approach has played a pivotal role in solidifying the team's influential position within the French research community, as evidenced by their active involvement in networks like FHU Pacemm and the establishment of Cirral cohort. The recent relocation of the team to the Paris-Saclay campus presents significant opportunities for enhanced collaboration with neighbors research groups and industry partners. Moreover, the team's focused research on microbiota and lipid-related mechanisms in liver diseases aligns closely with current biomedical research priorities. In this regard, the team covered a broad and convincing spectrum of descriptive and mechanistic studies using clinical, animal and in vitro models. In addition, the team is invested in related research fields (bariatric surgery, biobanking) and has established local and national collaborations and publications on microbiome-associated disorders (depression (with Moods Team UMRS 1178/Cesp, Ciocan D. et al. J. Psychiatry and Neuroscience, 2021), hypersensitivity (De Chaisemartin et al. Frontiers Immunology, 2024), pancreatitis (Ciocan, et al., Sci Rep 2018), vascularities (Desbois, et al. Sci Rep. 2021)). This strategic alignment not only enhances their scientific impact but also positions them favorably for groundbreaking discoveries in these critical areas, resulting in two publications closely aligned with Team1's main objective (ALD) and four publications in other areas. Financially, the team has successfully secured fundings, including support from multiple sources such as national grants (4 as leaders including 2 ANRs) and contributions from associated foundations (7 as leaders including 3 SNFGE and 2 Afef contracts). Regarding valorisation, 2 Cifre-Servier were obtained and one AAP- Satt maturation (410kE)

Weaknesses and risks linked to the context

Although the team is involved in collaborative projects beyond its focus area, they do not include substantial collaborations with the other teams, which seems like a missed opportunity, considering that the other teams' projects involve microbiome components, which could be expanded. Furthermore, the team faces several critical challenges and risks that could impact its trajectory and long-term success. Chief among these challenges is the difficulty in recruiting permanent scientific staff, which is essential for maintaining research continuity and expanding their scientific endeavours. Previous unsuccessful attempts to fill key positions underscore the competitive nature of recruitment in their field and highlight potential disruptions to research momentum. Currently, there are only six PhD students associated with the ongoing mandate, of whom three have already completed their dissertations. The remaining students are expected to finish their studies before the theoretical renewal date of the unit, which raises concerns about the sustainability of research activities and mentorship within the team. This limited number of PhD students may hinder the team's capacity for long-term research development and could impact its overall productivity and output. Additionally, only three permanent staff members hold an HDR, which further restricts the team's ability to supervise PhD students effectively: only 3 PhD thesis were defended. Additionally, while the relocation to Paris-Saclay presents promising opportunities, it also introduces risks associated with integrating into a new academic and research environment. Successfully navigating this transition will require effective management to leverage new collaborations and navigate administrative processes smoothly.

A significant area requiring improvement is the strategic positioning of their publications. Currently, there is a clear need to increase the number of publications in larger audience journals, particularly those that are strategically significant for advancing their field. The linkage between recruiting permanent staff, increasing

publication output, and securing research funding is crucial. The team has minimal responsibilities within scientific societies and does not actively participate in organising conferences, which may limit its visibility and opportunities for collaboration in the broader research community.

Analysis of the team's trajectory

The trajectory of Team 3, specialising in microbiome research within liver disease and alcohol use disorder, has experienced significant evolution under the leadership transition to AM Cassard. This shift has emphasised a blend of originality and significance at both fundamental and translational research levels. The team's research direction has expanded, particularly by delving into MASLD, and the team has identified new, related research areas that will help increase the team's impact (GP-1 agonists + alcoholic hepatitis, trauma + weight gain, somatic comorbidities of psychiatric disorders). The team's research direction remains highly innovative, particularly in exploring the role of intestinal microbiota and lipid-related mechanisms in liver diseases, although these two research areas are not strongly linked in the trajectory description. Their approach to identifying cofactors such as microbiota and lipids and elucidating the underlying mechanisms of disease progression is highly significant. By focusing on the interplay between microbiota and liver homeostasis, the team has unlocked novel insights into protective mechanisms involving dietary components like pectin and metabolites such as indoles. These findings have not only expanded the scientific understanding but also paved the way for potential therapeutic targets in ALD and MASLD. The team's ability to integrate these discoveries into clinical settings underscores their commitment to translating research into tangible patient benefits. Additionally, two ANR projects are currently underway, which are theoretically aligned with the new project and may further strengthen the team's research capabilities and output.

Regarding methodological strengths, the team employs a robust methodology that combines clinical expertise with advanced molecular and techniques (metabolomics/lipidomics), although the microbiological support, which could be helpful for mechanistic studies and to develop new (probiotics-based) therapeutics remains unclear. Their use of transgenic mouse models and in vitro systems to study the impact of microbiota on liver function exemplifies their methodological rigor. Moreover, collaborative efforts with national partners and the use of multi-omics approaches enhance the depth of their investigations. Team 3's trajectory, under the new leadership reflects a pioneering spirit in microbiome research, addressing critical gaps in understanding liver diseases from both basic science and clinical perspectives.

Without a substantial increase in impactful publications, the team may face challenges in attracting significant funding, thus impacting their ability to sustain and expand their research activities effectively. Moreover, there exists a noticeable gap between clinical and fundamental research publications. While the team's clinical research outputs are commendable, there is considerable space for enhancing fundamental research publications. Bridging this gap is essential to foster a balanced research portfolio that aligns with both clinical applications and fundamental scientific advancements.

RECOMMENDATIONS TO THE TEAM

Although the investment of the team into new collaborations outside of liver diseases is commendable, it should prioritize collaborative projects with the other teams. The team should prioritize enhancing its attractiveness to recruit and retain permanent scientific staff, particularly those with HDR. This could involve exploring new recruitment strategies, such as increased collaborations with renowned institutions, heightened visibility in international academic networks, and fostering a stimulating and collaborative work environment. Additionally, there is a pressing need to recruit more postdoctoral researchers and to supervise a greater number of PhD students, as this will enhance the team's capacity for research and development. It remains unclear how the new leader dual role as the leader of the unit will impact Team 3's research direction, particularly given the absence of permanent researchers aside from her. There is a clear need to intensify efforts aimed at publishing in high-impact journals strategically aligned with the team's research focus. This may require a strategic assessment of target journals and strengthening writing capacities to optimize the visibility and influence of the team's research endeavours.

Diversifying funding sources beyond national grants should be a priority by exploring opportunities for international partnerships, applying for EU fundings, and collaborating with industry. This could include a proactive strategy to respond to relevant European project calls. Importantly, such diversification will only be feasible with the recruitment of new personnel, including experienced postdoctoral researchers and permanent young scientists, who can drive these initiatives forward.

With the relocation to the Paris-Saclay campus, the team should seize this opportunity to optimize collaborations with neighbouring research groups and industry partners, requiring effective change management and adaptation to new administrative structures.

CONDUCT OF THE INTERVIEWS

Date

Start: November 04, 2024 at 08:30 a.m.

End: November 04, 2024 at 18:00 p.m.

Interview conducted: online

INTERVIEW SCHEDULE

8h45: Panel connected.
Presentation of the panel to the MI2 Unit.

9h00.Overview by the director (15 minutes).
9h15- Questions of the committee (15min).

9h30-11h00: Team presentations: 15min (10min past, 5min future) +15min questions
9h30: Team 1: Françoise Bachelerie / Géraldine Schlecht-Louf
"Immunoregulation, Chemokines and Viral Persistence"
10h00: Team 3: Gabriel Perlemuter/Anne-Marie Cassard
"Microbiome in liver disease: from susceptibility to treatment"
10h30: Team 2: Marc Pallardy / Saadia Kerdine-Romer
"Drug and Chemical Allergy, Immunotoxicology and Immunopathology"
11h-12h: Committee debriefing
12h-12h30: Meeting with the administrative and technical staff (ITA)
12h30-13h30: Lunch of the committee

13h30: Connection of the committee

13h45-14h15: Meeting with the students/post-docs
14h15-14h45 : Meeting with the researchers (team leaders are excluded)
14h45-15h30: Debrief of the committee:Time for discussion with lab members if needed

15h30-16h00: Meeting with the managing bodies:
Université Paris Saclay: Anne- Hélène Monsoro-Burq
Inserm: Philippe Arhets and Frederic Altare
Faculté de médecine: Eric Deutsch
Faculté de Pharmacie: Elias Fattal
16h-16h30: Preparation of the questions to the heads of the lab (past, future)

16h30-17h00: Questions to the directors (past and future)
17h-18h30: Meeting of the committee to finalize the report.

PARTICULAR POINT TO BE MENTIONED

NA

GENERAL OBSERVATIONS OF THE SUPERVISORS

Observations de portée générale à l'évaluation Hcéres

DER-PUR260024965

MI2 - Inflammation, Microbiome, Immunosurveillance

Madame, Monsieur,

L'Université Paris-Saclay et l'INSERM remercient le comité pour son travail qui met en lumière les atouts et éventuels points d'attention de l'unité MI2 « Inflammation, Microbiome, Immunosurveillance ».

Les tutelles n'ont pas de commentaire particulier sur ce rapport très complet.

Vous trouverez ci-joint les remarques proposées par la direction de l'unité.

Veuillez agréer Madame, Monsieur, nos sincères salutations.

Anne-Hélène Monsoro-Burq
Vice Présidence Recherche et Valorisation
Vice-Présidente Recherche déléguée Santé et Sciences de la Vie
Université Paris-Saclay

MI2- INSERM UMR-996

Inflammation, Microbiome and Immunosurveillance

MI2- UMR INSERM - Paris-Saclay University

Orsay, December 10th 2024

GENERAL COMMENTS ON THE EVALUATION REPORT

1- Predation of the journals of the MDPI group was officially exposed including Inserm communications. Consequently, we have stopped submitting at the end of 2021 with the exception of MS that were already on a long-term engagement.
2- Criticizing us for publishing in journals "*considered of low quality by governing bodies including Inserm*" in reference to the Frontiers journals is not acceptable in several respects:
   - First, we have never been officially informed by any governing body, including Inserm, that Frontiers journals are no longer considered recommendable,
   - Importantly, we use the tools provided by Inserm to select the journals where to publish (Clarivate, Journal Citation Reports™), with the objective of valorizing our work and that of our students and so far, the Frontiers journals are still there,
   - This ranking seems to be very recent, based on the lists we were able to find; one from June 2023 listing the "recommendable non-predatory journals", including all Frontiers ones, and the most recent list from October 2024 ("recommended journals"), where almost all Frontiers journals were banned (with the exception of *Frontiers of Hormone Research*),
   - So, apart from the fact that the mention that this ranking is based on "limited peer reviewing" is questionable, it cannot be applied retroactively to papers published before October 2024. Moreover, the October 2024 list ("recommended journals") cannot be used for this evaluation, which is tacking in consideration publications listed between 2018 and 2023.
   - Last, but not least, Inserm and HCERES have signed the "DORA" charter (https://www.inserm.fr/actualite/evaluation-recherche-inserm-signataire-declaration-san-francisco-dora/), which, among other things, refers to the need to put an end to the use of journal-based indicators, such as impact factors, in funding, appointments and promotions.
3- In terms of success, we would like to mention that, since the oral presentation of the unit, the project on the role of the intestinal microbiota in alcohol use disorders coordinated by the Team3 in framework of the PEPR-SAMS, has been approved.

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

Evaluation · Research · Higher Education
Hcéres

19 rue Poissonnière
75002 Paris, France
+33 1 89 97 44 00