Research evaluation

EVALUATION REPORT OF THE UNIT

IMVA-HB - Immunologie des maladies virales auto-immunes, hématologiques et bactériennes

UNDER THE SUPERVISION OF THE FOLLOWING ESTABLISHMENTS AND ORGANISMS:

Université Paris Saclay

Commissariat à l'énergie atomique et aux énergies alternatives - CEA

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

EVALUATION CAMPAIGN 2024-2025

GROUP E

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High Council for evaluation of research and highter education

In the name of the expert committee:

Michel Moutschen, 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 Michel Moutschen, université de Liège - CHU de Liège, Belgique
Experts:	Ms Leïla Belkhir, Cliniques universitaires Saint-Luc, UCLouvain, Belgique Mr Jérôme Estaquier, université de Paris (representative of Inserm CSS) Mr Rikard Holmdahl, Karolinska Institutet, Sweden Ms Marie-Laure Plissonnier, Inserm, Lyon (supporting personnel) Ms Aurore Rozieres, université Claude Bernard Lyon 1 (representative of CNU) Ms Martina Valentini, université de Genève, Suisse

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Ms Birke Bartosch

REPRESENTATIVES OF SUPERVISING INSTITUTIONS AND BODIES

Mr Étienne Augé, UPS
Mr Franck Dufour, Inserm
Ms Alexandra Fuchs, UPS
Mr Marc Humbert, UPS
Ms Simone Mergui, CEA
Ms Laurence Parmentier, Inserm

CHARACTERISATION OF THE UNIT

- Name: Immunologie des maladies virales auto-immunes, hématologiques et bactériennes
- Acronym: IMVA-HB
- Label and number: UMR1184
- Number of teams: 5
- Composition of the executive team: Mr Roger Le Grand (director) & Mr Frédéric Ducancel (deputy director)

SCIENTIFIC PANELS OF THE UNIT

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

THEMES OF THE UNIT

The unit is made up of five teams focusing on a) the pathogenesis of infections (especially viral), their transmission and their prevention by vaccines or antiviral drugs; b) persistent viral infections (especially HIV); c) autoimmune diseases (especially Sjögren's and rheumatoid arthritis); d) haematopoietic stem cells (both fundamental and therapeutic aspects); e) antibiotic resistance.

The unit also includes six core facilities, including several platforms. These core facilities support the research teams but have their own autonomy for external services and research into their own development.

HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

The UMR1184 results from the association of scientists of UMRE1/Division of Immuno-Virology located at the CEA of Fontenay-aux-Roses (FAR) research center, a joint research unit of CEA and université Paris-Sud (now UPS), and scientists of the U1012, a joint research unit of université Paris-Sud and Inserm, located at the school of medicine at Bicêtre university hospital. In 2020, the unit enriched its expertise and programs by integrating two new research teams on "Hematopoietic Cells and Therapeutic Applications" (LCSAT) and on "Multidrug resistant pathogens" (ReSIST).

UMR1184 is hosted in a dedicated building inaugurated in 2018 (IDMIT building) covering 5 141 m^2 of offices and labs. The UMR labs include conventional labs, BSL2 labs (659 m^2) and two BSL3 suites (357m^2 + 60 m^2), equipped for microbiology and immunology research programs.

The CoVir, LAID and ReSIST teams are based in a new 8,000 m^2 building inaugurated in 2022 on the historic Bicêtre site.

RESEARCH ENVIRONMENT OF THE UNIT

The unit provides an outstanding platform for doing cutting edge research. The NHP platform turned out for example to be useful for the covid research. The unit also has the advantage to incorporate both clinical and basic research-oriented groups and this is also a quite unique setting today.

The Medical School of Bicêtre in one of the largest University Hospital in France with a strong research activity in immunology and infectious diseases, representing a strong asset for UMR1184 translational medicine ambition.

The UMR1184 is a Department of the "François Jacob Institute of Biology" (IBFJ, approximately 600 scientists and administrative staff) of the DRF. The creation of this Department in 2016 represents a decisive asset for the unit sustainability and attests to the strong commitment of the CEA to support the ambition and missions (INBS) of the UMR. The IBFJ develops research programs focusing on human health providing an exceptional environment for the UMR1184, the other IBFJ departments strongly complementing the capacity of the structure (http://jacob.cea.fr/drf/ifrancoisjacob): microscopy (iRCM department), the outstanding radiochemistry and in vivo imaging facilities of NeurATRIS infrastructure (MIRCen department) and the state-of-the-art technologies for genomics of the "Centre National de Recherche en Génomique Humaine" (CNRGH department). Importantly, the François Jacob institute (IBFJ) at Fontenay-aux Roses CEA site has a strong activity on preclinical research, particularly using NHPs for neurodegenerative diseases and prion diseases, in addition to UMR1184 programs on infectious diseases.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	14
Maitres de conférences et assimilés	13
Directeurs de recherche et assimilés	3
Chargés de recherche et assimilés	4
Personnels d'appui à la recherche	61
Sous-total personnels permanents en activité	**95**
Enseignants-chercheurs et chercheurs non permanents et assimilés	3
Personnels d'appui non permanents	34
Post-doctorants	0
Doctorants	35
Sous-total personnels non permanents en activité	**72**
Total personnels	**167**

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
CEA	0	0	49
U Paris Saclay	27	0	5
Inserm	0	6	7
Autres	0	1	0
Total personnels	**27**	**7**	**61**

GLOBAL ASSESSMENT

The unit has set up in vivo molecular imaging techniques (NHP) to develop its capacity to monitor infections and diseases (PET-CT in BSL3). The unit's main scientific results concern the evaluation of a vaccine against CHIKV (JCI Insight 2022), the description of antivirals, and protection or vaccination against Zika and SARS-CoV-2 viruses in non-human primates (Nat Comm. 2021, 2022; Cell 2021; Nature 2020). More than 650 manuscripts have been published by the unit. Several members of the unit are involved in the organisation of national and international congresses (fourteen events), participate in scientific organisations or councils (ANRS-MIE, Sidaction, CA-SFM, ESGARS, EUCAST, European Leukemia Net, SFTCG, CSS5 Inserm, etc.), have been invited to give lectures (UK, USA, European Commission) or have received awards (e.g. Chevalier de l'ordre national du mérite). The current DU is a member of the Académie des Médecins Vétérinaires, and the future DU is vice-dean of the UPS medical school. The unit has welcomed 70 PhD students, some of whom have been awarded prizes or scholarships for international conferences and courses (KeyStone conference, FRM, Société Française de Cytométrie, summer school on advanced immunology) and eleven HDRs were defended during the period. The unit has a total average annual budget of around €16 million, of which around 60% comes from external grants (87 grants in total, including 47 as PI), including the European agile network for medical measures to combat CBRN, the IHU promotheus, and numerous other international, European and national grant sources. However, no ERC grants have been obtained.

The industrial sector accounts for around 25% of external resources (collaboration programs or paid services with start-ups (Axenis, Adjuvatis, InnaVirVax, etc), SMEs (Themis, Valneva, Polymun, etc.) and large pharmaceutical companies (GSK, Sanofi Pasteur, Janssen, Merck), and includes collaborations on in vivo imaging of vaccine antigens and characterisation of long-term immune memory mechanisms (Sanofi Pasteur) as well as in vivo visualisation of antiretroviral drug distribution using PET-CT technology (ViiV/GSK). The unit has filed six patents and has strong clinical links thanks to its activity in the field of infectious and autoimmune diseases.

DETAILED EVALUATION OF THE UNIT

A - CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

- Implement a publication policy that involves platform technicians and scientists to a greater extent, so as to highlight their essential role in the projects.

UMR1184 responded by explaining that its publication policy was compliant with the McNutt et al. 2018 standard. This includes thanking all those involved in the 'Acknowledgements' section. However, the unit does not specify the proportion of its articles in which platform scientists are bona fide co-authors and does not explain whether a proactive approach has been taken to encourage these scientists to become involved in the design and proofreading of articles.

- Involve patients and patient organisations in the unit's research and in the exploitation of discoveries.

The unit explains that patient associations are not represented on an advisory board, but that they are present in the structures with which the unit interacts closely (such as the Prometheus Institute, the ANR and the ANRS). It also explains that several of its scientists are part of consortia in which patients are represented. This demonstrates that the culture of societal and inclusive research is very much present in UMR1184, even if patients are not directly represented.

- improve gender balance

UMR1184 has created deputy team leader positions for four of its five teams. Three of these positions are held by women. In addition, the Executive Committee includes three women out of a total of six members. We can assume that the gender equality policy covers many other aspects in a structure as large as the UMR1184. Specific questions will be asked.

- strengthen interaction between staff from different platforms, including via a 'platform day'.

The unit explains that such an event has been organised, but does not specify what the situation is in terms of day-to-day interactions between platforms. It can be assumed that the 'core lab leaders committee' is an effective means of encouraging these interactions.

-extend the 'PhD/postdoc day' format into a 'retreat-like' format.

The unit explains that this has been organised at Fremigny.

- pay attention to the workload of platform staff.

The unit explains that it has implemented ISO9001 standards but does not specify which indicators are used or how these have changed over the last two years.

- The committee recommended for more synergies between the five teams that make up UMR 1184, as well as more interaction with national and international academic and industrial partners.

The UR responded convincingly, explaining that seeding grants have been proposed to generate new initiatives between the different teams. Participation in Covid-19 research projects and in the RHIVIERA and Prometheus consortia involves all of the UR's teams. Industrial collaborations are described below.

Overall, the research unit has taken account of the recommendations for action.

B - EVALUATION AREAS

Guidelines for all areas of evaluation (1, 2, 3 and 4): Considering the references defined in the unit's evaluation guidelines, the committee ensures that a distinction is made on the outstanding elements for strengths or weaknesses. Each point is documented by observable facts including the elements from the portfolio. The committee assesses if the unit's results are consistent with its activity profile.

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

Assessment on the scientific objectives of the unit

"Excellent"
The scientific objectives of each team are entirely relevant and adapted to the current state of knowledge and the challenges facing society. They are also appropriate in terms of the platforms available. The unit's interdisciplinary potential is evident in the involvement of all the teams during the pandemic and in their joint participation in the sepsis project. However, during the oral presentations by each team leader, this aspect remained not detailed enough.

Assessment on the unit's resources

"Outstanding"
The unit has a highly qualified staff (159 FTEs), 40% of whom hold permanent positions. With its unique technological platforms, and its clinical research unit at Bicêtre, the unit has the resources to carry out very high-level translational research.
An important new technology area needed is genetic modification of mice, this could bridge different groups and also translate to humans and NPH. A core facility dedicated to gene editing and viral victors could be envisaged.

Assessment on the functioning of the unit

"Very good to excellent"
The unit has to deal with structural features that make its organisation and operation quite complex (two sites, three supervisory institutions, the dual mission of the core units). Given these constraints, the unit has put in place an efficient governance with different committees and management teams.
However, a number of problems remain (autonomy of the platforms, role of GPE, development of a common culture, internal communication, support in setting research projects, integration of doctoral schools with the unit). This will be discussed below.

1/ The unit has set itself relevant scientific objectives.

Strengths and possibilities linked to the context

These are very strong research themes that are conducive to fundamental, inter/transdisciplinary and translational developments.

Infectious diseases (particularly pandemic diseases), sepsis and antibiotic resistance are major scourges for humanity and are more than ever a public health priority. The same applies to inflammatory and autoimmune diseases, given a number of factors such as the ageing of the population and the use of new cancer immunotherapies.

Weaknesses and risks linked to the context

Although the scientific objectives, state of knowledge and societal needs are described in each team's self-assessment, it is regrettable that the unit's own report remains relatively vague in this respect. The rationale for grouping the various teams together and their synergies have not emerged during the evaluation process. The scientific strategy is first and foremost defined by each team leader and then validated by a whole series of bodies. Scientific objectives are primarily dictated and influenced by a series of interactions with the many supervisory authorities, but are not part of a structured and specific strategic plan for the unit. Given the structural heterogeneity of the unit, the absence of such an integrated strategic plan risks to increase the remoteness of each of the teams and encourage incremental siloed research.

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 number, specificity and quality of the unit's human resources are appropriate. The ratio of core facilities staff to research team staff seems appropriate, as does the age pyramid. The diversity of funding sources and the increase in the proportion of non-academic (20%) and European (31%) funding is also a strength for the unit. The filing of seven patents since 2020 is also a strength and demonstrates that technology transfer is effective.

Some elements:

-49 new FTE were recruited during the five last years (UPSaclay, CEA and Inserm)

-the department hosts 159 people corresponding to 139.8 FTEs, among which 41% are on permanent position

- 98 research projects including 14 EU collaborative programs, 19 projects funded by ANR and 16 contracts with private partners

-coordinated or co-coordinated 1) The RHIVIERA consortium on characterization of HIV viral reservoirs and development of strategies for better control of infection. financially supported by ViiV Healthcare, fondation MSD Avenir, ANRS-MIE and NIH; 2) The IHU Prometheus on Sepsis (40M€) 3) The Counteract program on medical countermeasures against CBRN threats financed by the European Defense Fund project 4) The NECESSITY IHI project on "New clinical endpoints in primary Sjögren's syndrome"

The number of partnerships and programs realized between 2019 and 2023 increased of 33.7%, among which 75%-83% involved academic institutions. This results in a 18% increase of external resources (9.1 M€ to 11.1 M€). In addition, the unit interacts with non-academic partners (see section 3-1 Area 4) accounting for up to 26% of the external resources.

Weaknesses and risks linked to the context

There are currently 43 FTEs dedicated to the operation of core facilities. Of these, only 22 have permanent contracts. Technology platform staff are often highly qualified and much sought after by biotech firms. Their stability is crucial to the UMR's future. Specific questions were asked prior to the visit to the unit. Reassuring answers were provided regarding stabilisation of 8-9 positions between 2025 and 2029 to secure most of the critical activities (technical, safety and lab management, and support), which are all in the plans discussed with institutional bodies.

The relationship between the research teams, the core facilities and the GPE remains somewhat unclear. The need for the GPE is clear, given the external missions of the core facilities and the subsequent need for rigorous planning. However, we did perceive a threat of a possible incompatibility between the way the GPE operates and the essential fluidity of fundamental research. Scientific creativity is based on direct, continuous and reactive interaction between researchers and the technological tools that enable them to generate and analyse data. This interaction is crucial to the exploration of new ideas, the rapid adjustment of experimental protocols and the unexpected discoveries that are often the source of the most significant breakthrough. Our fear is that a certain rigidity in planning could slow down rapid adjustments, lead to a loss of immediacy, and above all fragment research by limiting researchers' immersion in their projects.

Another fear linked to this point is that the need for standardisation of core facilities (to meet the expectations of external users) is incompatible with a certain versatility necessary for fundamental research.

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 executive committee (EXCOM) has been created to guarante an integrated organization management since the UMR1184 is located in two different sites, CEA campus at Fontenay-aux-Roses and at Bicêtre Hospital. Members of the EXCOM include two site referent scientists to foster communication between research groups and the EXCOM. This committee takes strategic decisions for the unit governance and it is assisted in the unit management by several internal services. Safety management is an UMR priority and ISO9001 certification was obtained for the core lab activities. The organization is well defined, with a dedicated manager and including 13 processes (e.g. administration, scientific and bio-informatic support). Moreover, GPE process with 11 FTEs coordinates all the processes, reviews projects and organize the interactions between the UMR partners, PI and core lab activities. The technological platforms play an important role in this unit, both in terms of technical expertise and the human resources allocated to these platforms. The support from the CEA is strong in order to maintain these core lab facilities.

To notice, discussion has been started to improve the environmental impact of the UMR. Concerning the prevention of psychosocial risks, training courses had been provided by the Institutions to group leaders and team members. The unit has as well specific actions to improve management and workload in order to prevent psychosocial risks. In addition, a program to promote women leadership is available.

Weaknesses and risks linked to the context

No details were given of the members' affiliations and gender parity regarding the executive committee. How many staff members attended to the "OSER" program? The work on environmental impact is preliminary and requires consolidation. The functioning of the GPE has not been clearly explained: do the platform managers have decision-making power in scientific projects? It is not clear if the GPE manages as well the ethical considerations of the protocol and specific declarations such GMO or CODECOH.

EVALUATION AREA 2: ATTRACTIVENESS

Assessment on the attractiveness of the unit

The attractiveness can be considered **excellent**, in particular due to the staff support policy, the diversity of fundings and the quality of the technological 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

The UMR has unique equipment, technologies and platforms. BSL2/3 NHP facilities have a total housing capacity of 530 NHPs. The BSL2 (230 NHP) and BSL3 (219 NHP) are equipped with state-of-the-art materials and instruments for surgery, endoscopy, colposcopy and necropsy. The in vivo imaging suites are equipped with a two-photon microscope and whole body positron emission tomography couple to X-ray scan (PET-CT, Vereos, Philips), both adapted to NHPs and in BSL3 containment. Since 2023, the unit has access to 350m2 of BSL2/3 suites (cooperation with NeurATRIS and MIRCen) in order to complement NHP studies. The technologies available within the core lab facilities are cutting-edge and unique in Europe. Such a concentration of equipment contributes to the UMR's attractiveness as a whole. It is also important to note that integrated management of these facilities helps to improve the quality of their operation and also helps to attract partnerships with other research institutions and private companies.

There are indeed 98 contracts within the quinquennial, 87 of which are academic, representing approximately €8 million just in 2023. Of these contracts, the UMR is the project leader in around 60% of cases.

The result is an apparently healthy budget, which is invaluable given the threats to university research funding.

An indication of the UMR's attractiveness is the number of doctoral theses that have been successfully completed (>70), the number of HDR (Habilitation à diriger les recherches) theses (11) as well as the recruitment of seven researchers.

The UMR's scientists are frequently invited to prestigious and selective international conferences, sit on the editorial boards of good scientific journals and have received numerous international awards.

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

To properly assess the geographical aspects of this attractiveness, it would be interesting to know the universities from which the PhD students hosted by the UMR come. Similarly, no information is provided on post-doctoral researchers and their origins. It is also surprising that, given the attractiveness of UMR1184, there are no ERC grant winners on the staff. Indeed, ERC grant winners have the option of joining the research unit of their choice within the European union, while retaining the various benefits of the grant. Standard 2 'Quality of staff support policy' is not really described in the self-assessment document. What has been put in place in terms of support for writing and setting up complex projects (such as ERCs), project management, administrative simplification, etc.? This information is lacking for a precise evaluation of strengths and weaknesses of the standard.

Most of the platforms are located at the CEA site, and the geographical distance makes it difficult for the research teams at the Bicêtre site to access them, which led them to develop their own core lab facilities.

EVALUATION AREA 3: SCIENTIFIC PRODUCTION

Assessment on the scientific production of the unit

The quality of the unit's scientific output (as distinct from that of the various teams) can be considered as "excellent". It is regrettable that there were not more publications involving several of the UMR's teams. Nevertheless, the UMR has published high-quality work which has influenced the recommendations for treatment by Covid-19. This demonstrates the UMR's great responsiveness and its ability to meet societal challenges. The other criteria that define the quality of a scientific production according to COARA standards are unquestionably met.

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 five publications presented in the unit's portfolio (from 2020 to 2022) are published in prestigious journals (including Cell and Nature). These are works carried out in collaboration with other French or international research institutions, or with industrial partners. Scientists from UMR 1184 are the 1st or last author. This illustrates the quality of the network of which the unit is a part and the leading role it plays in it. We appreciate that the scientific staff of the core facilities are involved in these publications, including as first authors. The journals in which this work has been published are renowned for their high standards of ethics and integrity.

The five articles in the portfolio are innovative in terms of the research themes and the complementarity of the methodological approaches used. The five articles highlighted by the unit concern emerging infectious diseases, which can be assimilated to a 'one health' theme, which is clearly an opportunity for the coming years.

If we consider all the publications of all the teams that make up the UMR, it is abundant (>850 articles) and seems proportional to the number of scientists in the UMR. Many high-quality articles are the result of collaboration between LIT and LCoVIR, as well as between LCoVIR and LAID. On the other hand, the other two teams (LReSIST and LCSAT) have few or no joint publications with the other teams in the UMR.

Major scientific contributions over the last five years include work on the pathogenesis of Sjögren's disease, the positioning of antiviral and immunomodulatory treatments in covid, work on elite controllers in HIV infection, and the pharmacokinetics and tissue distribution of key drugs in the treatment of HIV infection. The LReSIST team has also made significant contributions to antibiotic resistance, both in terms of developing new diagnostic tools and understanding the structure-function relationship of carbapenemases. We should also mention the pioneering work of the LCSAT team in the treatment of haemoglobinopathies and myeloid haemopathies.

In more than 60% of the publications reported, UMR members are either first or last authors. As explained above, the recommendations on autorship seem to be respected. The scientific journals in which the work is published are often among the most prestigious (journals from the Nature group, for example). It is difficult to know whether the unit is fully compliant with European Union recommendations to facilitate access to publications via an institutional directory. The HAL link is only provided for around sixty articles, which is not very many given the total number of publications.

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

As already pointed out in the previous evaluation, it is likely that regulatory, ethical, societal and budgetary constraints will affect the use of such models in the coming years. It is therefore essential that the teams that mainly use these models within the UMR explore alternative approaches now (e.g. in silico, organoids, organs on a chip, etc.). Another threat is the fragmentation of the different research themes within the unit. New, themes that encourage interaction between the different teams are lacking.

EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

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

The contribution of research activities to society can be considered **excellent**. The unit maintains strong collaborations with non-academic partners, including leading pharmaceutical companies, SMEs, and startups, which account for 25% of its external funding, driven by the generation of patents.

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 collaborates with two contract research organizations, Oncodesign-services and Life&Soft in order to facilitate the unit's capacity to interact with industrial partners and to extend the services offered to the scientific community. The unit has established strong collaborations with non-academic partners, including leading pharmaceutical companies, as well as SMEs and startups, which account for 25% of its external resources. It is also committed to further developing mid- and long-term partnerships with the non-academic sector, particularly through two collaborative projects initiated during the current contract with Sanofi and GSK. One of these projects includes the first clinical evaluation of Dolutegravir biodistribution.

The fundamental research conducted by the unit has resulted in the generation of six patents, as well as the filing of intellectual property rights for BatLAB with the Program Protection Agency, underscoring the laboratory's strong commitment to data valorization. To further support this effort, the unit recruited a full-time staff member dedicated to this function at the end of 2023.

Industrial contracts represent 16% of the contracts of UMR1184 over the period, including Startups Axenis, Adjuvatis, InnaVirVax, Imchek Therapeutics, Anokion, Kanyos, Osivax, Life&Soft), SME (Themis, Valneva, Polymun, Oncodesign services, BioMarin) and large pharmaceutical companies (GSK, Sanofi Pasteur, Janssen, Merck). These contracts account for 26% of the unit's external resources.

In addition, the unit has made significant strides in enhancing its visibility through scientific outreach activities. These efforts include presenting its discoveries related to Covid-19 treatment, the role of vaccines in infection prevention. The unit's work has been communicated through various media outlets, including Agence France-Presse, France Inter, France Culture, national newspapers such as Le Monde, scientific journals like *La Recherche*, scientific seminars, and even YouTube videos.

One of the strengths of the unit is its development of an environment that combines clinical research with rare expertise and capabilities in preclinical research and technological development. The teams are developing fundamental and translational disease-oriented research programs, focusing on cell-restriction factors in response to infections, pathogen characterization, mucosal immunity, the interplay between innate and adaptive immune responses in natural responses to infections and autoimmune diseases, as well as hematopoiesis in the myeloid immune compartment. The ultimate goal is vaccine and therapeutic innovation, as well as diagnostic and technological advancements, as demonstrated during the Covid-19 pandemic.
This investment in clinical research is a common feature across all the unit's teams, which has led the unit to initiate several dozen clinical studies.

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

Although the unit is already associated with several patents, their valorization and application remain ongoing tasks and will be further developed in the next contract.

The unit has made significant efforts to increase its visibility with the general public through various communication channels. However, despite the strong connection to human diseases, little information is available in the document regarding potential links with patient associations.

ANALYSIS OF THE UNIT'S TRAJECTORY

Over a period of five years, the unit has generally pursued a trajectory of excellence. It has maintained a high level of first-quartile publications and a balanced budget, thanks in particular to contracts with the private sector. The comments made in the previous evaluation have generally been taken into account. The pandemic has provided an opportunity for research involving the various teams, demonstrating the unit's agility. Despite this favourable trajectory, the committee felt that efforts still needed to be made to integrate the various teams, in particular through the emergence of a common culture, the definition of new research themes with a high societal value (e.g. cooperation with developing countries, One Health theme), and cross-disciplinary support for researchers from all the units. The unit is about to undergo major changes, in particular with the change of its director. This change is likely to shift the unit's center of gravity towards translational or clinical research. This is undoubtedly a source of opportunities, but it is also a source of concern, as we saw during our visit. The committee is confident that the new director will be able to maintain the excellence of the various teams and technological platforms while facilitating the integration mentioned above. His concern for ethical values and the well-being of the scientific, technical and administrative staff, which was explicitly stated during the presentations, will be a key factor in this transition.

As for the individual trajectory of each team:

LIT has maintained a strong balance between basic and translational research with focus on vaccine mechanisms, host-pathogen interactions, and expansion into new areas, such as parasitic diseases, HSV-1 and Covid-19 infections. It increased its collaborations with international consortia, has maintained a high number of publications and strengthened its global visibility. Future challenges to cement the team as leader in immunology and infectious diseases will be increasing its visibility for its independent discoveries, recruiting postdocs, improving gender balance, and participating more in clinical research.

CoVIR will keep its current focus on the mechanisms of pathogens persistence and reinforcing their research by using tissue-specific approaches in particular related to tissue microenvironment using both humans cohorts and NHPs. Pathogens will be extended to tuberculosis, S pneumoniae and respiratory viruses in the lungs, which falls in line with the goals of the IHU sepsis. However, given the size of the group and the new responsibilities of the PI, a risk of dispersion exists.

LMAI has a long terms outstanding track record standing focusing on clinical research of RA and SjD based on its clinical cohorts, epidemiologic analysis, analysis of laboratory and clinical parameters, helping industry for validating new treatments and also initiating new treatments of already established drugs. With the development of novel treatments for these diseases that are becoming available, the focus of the team is now shifting towards earlier steps of the diseases such as identification of targets for preventive and curative treatments.

LReSIST team has made important contributions to antimicrobial resistance research with high-quality publications, patents, and recognition in the scientific community. Partnerships with biotech companies and clinical labs have also boosted the practical impact of the team's research. While their core project on carbapenemases will remain impactful, expanding into areas like the microbiome and sepsis risks stretching the team's resources too thin and will require recruitment of permanent senior researchers.

RECOMMENDATIONS TO THE UNIT

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

The organization of the unit seems complex, primarily due to the different geographically distant sites, as well as the existence of multiple supervisory bodies, which raises concerns among the technical staff. Communication needs to be improved between the different teams, and the presentation of research projects should be organized for all unit members in both English and French, so that the technical staff can fully understand the projects (due to issues with English comprehension). With its highly developed core lab facilities, the unit possesses unique technological expertise with many contracts dedicated to the platforms. However, this seems to be at the expense of recruiting support staff for the research teams.

The committee believes that efforts should be made to encourage new 'non-incremental' research involving all the UMR teams. Involvement of other sectors (such as humanities) should also be developed further.

Recommendations regarding the Evaluation Area 2: Attractiveness

The unit's attractiveness is excellent, largely due to the quality of its scientific output and its unique range of technological platforms. However, there are relatively few junior researchers (particularly post-docs). Similarly, the absence of ERC holders is somewhat questionable, as these awardees have the opportunity to choose their research environment. We believe that the unit's attractiveness could be improved by providing better support for young researchers (simplified access to platforms, help in setting up European projects) and by establishing an interdisciplinary and collaborative culture within the unit. The unit's impact and societal relevance could also be made more visible by carrying out more clinical studies, facilitating technology transfer and highlighting themes such as One Health and cooperation with developing countries.

Recommendations regarding Evaluation Area 3: Scientific Production

The unit's scientific output is excellent, both in terms of content and choice of scientific journals. In the same vein as the observations made in the previous sections, it is surprising that the unit's five teams mention different affiliations in their scientific articles. In some cases, UMR1184 is not even mentioned. The unit's visibility should be improved by standardising the affiliations given in the articles. As mentioned above, all the articles published by the unit should be on the HAL of Paris Saclay with an indexing system that makes it possible to identify the unit's output.

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

The original organization of this unit, structured around technical platforms, is conducive to the generation of patents, for which the effort of valorization should be continued.

TEAM-BY-TEAM ASSESSMENT

Team 1: Immunity and transmission

Name of the supervisor: Mr Roger Le Grand

THEMES OF THE TEAM

The LIT team focuses on mechanisms of pathogen transmission, host response, and prevention strategies, with particular emphasis on vaccine mechanisms of action. This includes exploring mucosal immunity, systemic responses, and developing novel preventive measures against infectious diseases.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team is encouraged to maintain the outstanding activities exemplary combining basic research and translational studies and the excellent quality of their scientific output. In this respect, the committee welcomes the arrival of two clinical researchers as additional strengthening of the team which is reassured to even increase its visibility at the international level.

LIT Team's Actions:

- The team continues to deliver high-profile publications, contributing to advancements in vaccine mechanisms and pathogen-host interactions.
- The team has sustained its scientific excellence while expanding its international recognition through strategic collaborations (ex: RHIVIERA consortium)

The committee applauds the management skills of the team leader for the fast set-up of the new FAR site research facilities. Gender balance should be actively pursued if passive processes are not working.
The team could increase the number of PhD training in the future considering the number of members with HDR.

LIT Team's Actions:

- Gender balance initiatives have been partially addressed, with ongoing efforts for improvement.
- The team has made progress in its organizational structure and has improved mentoring, training, and integrating young researchers.

The team should make a particular effort in integrating into the team project, the 2 novel research aims (Parasite diseases and HSV-1 infection).

LIT Team's Actions:

- Work on parasitic diseases and HSV-1 infections is ongoing, supported by collaborations within the unit and access to advanced preclinical models.
- The team is allocating resources and leveraging its infrastructure to accommodate these new research themes without compromising existing projects.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	4
Maitres de conférences et assimilés	0
Directeurs de recherche et assimilés	4
Chargés de recherche et assimilés	3
Personnels d'appui à la recherche	0
Sous-total personnels permanents en activité	**11**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	5
Post-doctorants	2

Doctorants	12
Sous-total personnels non permanents en activité	**19**
Total personnels	**30**

EVALUATION

Overall assessment of the team

The LIT team is very strong in preclinical research and collaborations, with a solid record of publications and partnerships. Improving recruitment of postdocs and focusing more on clinical research and vaccine discovery could further boost its impact. Overall, the team deserves an excellent score.

Strengths and possibilities linked to the context

The LIT team is composed of several permanent researchers including two DR CEA, one DR2 Inserm, one DR2 CNRS, one CRCN Inserm, two researchers (CR) CEA, one PU, and three PUPH. The non-permanent staff of the team includes 12 PhD students, two postdoctoral researchers, four engineers and one technician.

The LIT team demonstrates excellent visibility within the scientific community, reflected in their numerous contributions and recognitions. Members of the team have been invited to speak at international conferences such as AIDS International Conference, CAPRISA-FEMIN workshop or World Ophthalmology Congress. They have also contributed to the organization of national and international workshops on innovative preventive strategies for infectious diseases.

The team's researchers actively participate in scientific committees and advisory boards. For example, one member for the unit contributes to the field of ophthalmology as a member of the Executive Committee and General Secretary of the French Society of Ophthalmology and as a member of prestigious organizations like EUCornea. One member for the unit is a co-founder of the FEMIN Network and office member of the ANRS-MIE AC53 IST and AC41 Basic Research, plays a crucial role in fostering collaborations on microbiota and infectious diseases. One member for the unit demonstrates leadership as the founder of the "Pediatric and Immunity" Network at the Société Française d'Immunologie (SFI), a member of the FEMIN Network, and an expert scientific adviser at IBFJ, CEA. Furthermore, Dr. Roger Le Grand serves as a deputy director of the Prometheus Institute, where he is in charge of scientific coordination, education, and valorization, highlighting his leadership in major translational and educational initiatives. The team is also involved in the RHIVIERA consortium co-coordinated by Roger Le Grand, which focuses on the characterization of HIV viral reservoirs and the development of strategies for better control of infection. This initiative exemplifies their leadership in addressing key challenges in HIV cure research.

The LIT team excels in integrating basic and translational research, focusing on vaccine mechanisms, pathogen transmission, and host immune responses. They effectively combine fundamental discoveries, particularly in the development and testing of vaccines using advanced preclinical models such as non-human primates, with clinical applications, bridging the gap between laboratory findings and real-world solutions. The team uses state-of-the-art platforms, including mass cytometry and PET-CT imaging, enabling high-resolution and impactful research.

Their consistent delivery of high-quality scientific outputs is reflected in over 200 peer-reviewed articles published in prestigious journals such as *Mucosal Immunology* (2022), *Nature Communications* (2023-2021-2019), *vaccines* (2021), *EBioMedicine* (2020), *Nature microbiology* (2021), *Antimicrobial Agents and Chemotherapy* (2020), *PLos ONE* (2019-2020). Their discoveries have significantly advanced knowledge in mucosal immunity, vaccine mechanisms, and pathogen transmission. For example, they demonstrated that broadly neutralizing antibodies (bNAbs) potently inhibit cell-to-cell transmission of HIV/SIV, providing a foundation for vaccine development and pre-clinical studies (EBioMedicine 2020, Nature Communications 2023). They also pinpointed the dynamics of immune responses to modified vaccinia Ankara (MVA)-based vaccines, showing that the inoculation route influences immune efficacy (Sci Rep 2018, NPJ Vaccine 2020, Front Immunol 2021). Additionally, their work highlighted the inhibitory effects of seminal plasma on Chlamydia trachomatis infection and its impact on SIV replication in colorectal tissues (Communications Biology 2021, Sci Rep 2024). Furthermore, insights into neonatal immune responses revealed the interplay between microbiota and CD4+ T cell development, advancing the understanding of immune mechanisms in early life (Front Immunology 2022).

Robust partnerships with academic institutions, industry, and international consortia significantly enhance their visibility and competitiveness. These collaborations have allowed them to secure numerous national and international grants, further validating their scientific excellence with more than 50 contracts including International Grants (EU HORIZON projects such as Flavivaccine, TracVac, and EAVI-2020), National Funding (ANR, PEPR-ANRS-MIE) and Philanthropic Funding (Grants from Sidaction, France Alzheimer, and other charitable organizations). These grants have collectively amounted to over €30 million during the evaluation period, underlining the unit's capacity to attract competitive funding and validating its scientific excellence.

The leadership of the LIT team has demonstrated excellence in managing resources, establishing new research sites, and integrating novel research directions. The recent setup of the FAR research facilities highlights their organizational efficiency. The team actively mentors PhD students and junior researchers, fostering their development and involving them in impactful projects. Over the evaluation period, the team has hosted a total of twelve interns, 29 PhD students, of which 14 successfully defended their theses. In addition, seven postdoctoral fellows were trained during this period. Several of them were coming from foreign countries (India, Thailand, Cameroon, Australia, Lebanon, Ireland, Portugal, Spain). Three of the PhD fellows, and one postdoctoral fellow, have been recruited as engineer/researcher (permanent position) at the CEA in 2018, 2021, 2022 and 2023 respectively.

The LIT team has been actively addressing emerging challenges, such as SARS-CoV-2. They have also included HSV-1 infections in their research and have also integrated parasitic diseases into their research focus. This adaptability highlights the team's capacity to respond to global health priorities while maintaining its high research standards.

In conclusion, the LIT team excels in its integration of advanced preclinical models, high-impact research platforms, and collaborative networks, solidifying its pivotal role in advancing immunology and infectious disease research. These strengths, combined with their adaptability to new challenges, emphasize their position as a leader in the field.

Weaknesses and risks linked to the context

The LIT team excels in preclinical and collaborative research, using advanced preclinical models and modern technologies. However, the team itself has identified some areas for improvement.

The NHP platform is crucial for the unit and Europe, requiring significant investment to maintain and develop. One notable gap is the lack of applications and success in securing ERC grants, which are pivotal for advancing ambitious, high-impact projects. Strengthening their ability to compete for such prestigious funding would help align their achievements with top-tier international standards.

The team also struggles with recruiting post-doctoral scientists, a critical resource for driving forward innovative and dynamic research programs.

Another area for improvement is the need to enhance translational research by increasing the use of human samples and expanding clinical studies.

Additionally, the team could better leverage its intellectual and technological resources by focusing more on discovery-driven vaccine research and concentrating on a few more targeted research themes. Increasing involvement in clinical studies, alongside vaccine development, would align their efforts with pressing global health needs and boost their visibility in the broader medical and scientific communities.

In summary, addressing these weaknesses—securing ERC grants, recruiting post-doctoral talent, and strengthening translational research—would enable the LIT team to enhance its impact and further reinforce its position as a leader in immunology and infectious disease research.

Analysis of the team's trajectory

Since 2019, the LIT team has successfully aligned with recommendations. It has made good progress in maintaining a strong balance between basic and translational research. It has continued to focus on vaccine mechanisms, host-pathogen interactions, and expanded its research into new areas, such as parasitic diseases and HSV-1 infections. They also show their ability to adapt to emerging scientific challenges with research focusing on Covid-19. The team has also increased its collaborations with international consortia, which has helped maintain a high number of publications and strengthen its global visibility.

While the team has made efforts to involve PhD students and junior researchers, attracting postdoctoral scientists remains a challenge. This could impact the team's ability to innovate and ensure continuity.

In summary, the LIT team has followed many of the 2019 recommendations, particularly in maintaining its research focus and improving infrastructure. Still, it faces challenges in achieving stronger visibility for its independent discoveries, recruiting postdocs, improving gender balance, and participating more in clinical research. Addressing these issues will further strengthen its position as a leader in immunology and infectious diseases.

RECOMMENDATIONS TO THE TEAM

Enhance postdoctoral recruitment. This will foster innovation and ensure leadership succession.

Increase involvement in Clinical Trials and patient societies: Actively participate in clinical trials to bridge the gap between preclinical research and real-world applications. Strengthen partnerships with patient societies, hospitals, biopharma, and patient societies to ensure research aligns with patient needs and improve visibility.

Maximize expertise for translational research: To maximize impact, the team could benefit from focusing more intensely on selected research themes, allowing for deeper exploration and impactful outcomes. Additionally, ensuring the sustainability of NHP trials is critical for maintaining the translational potential of their preclinical models. By prioritizing innovative projects that integrate preclinical findings with human-centered research, the team can further enhance its contributions to immunology and vaccine development.

Team 2: Control of viral infections

Name of the supervisor: Mr Olivier Lambotte

THEMES OF THE TEAM

LCoVIR team: A central scientific axis of this team is the mechanisms leading to the persistence of pathogens. Initially focused on HIV, their fields of interest have broadened to other infectious diseases including Covid-19, Influenza and tuberculosis. They use human cohorts (ANRS CO21 CODEX cohort; PRIMO cohort; OncoVIHAC cohort) developed by the unity core facility. The contributions of the team are related to (i) the understanding of immune control in HIV controllers (HICs) in order to develop HIV cure strategies; (ii) the role of adipose tissue in the persistence of pathogens and (iii) the immunomodulatory mechanisms favoring persistence of HIV/SIV and other pathogens.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

In the previous evaluation, one of the recommendations was to improve their capacity to obtain International and European grants in view of the scientific activities of the team. This part remains to be done as the financial resources remain limited.

Similarly, the questioning of two sites in term of communication and access of the platform was addressed and remains.

About the scientific strategy and the risk of adipose tissues as an outlier project, the team has developed some collaborations leading to publications. The risk is now the numbers of project proposed.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	4
Maitres de conférences et assimilés	3
Directeurs de recherche et assimilés	2
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	1
Sous-total personnels permanents en activité	**11**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	1
Post-doctorants	1
Doctorants	5
Sous-total personnels non permanents en activité	**7**
Total personnels	**18**

EVALUATION

Overall assessment of the team

The supervisor of the team is a well-known scientist in the HIV field and will be the new director of the Unit. The overall track record of the team is very good with major publications in the fields. The clinicians are also involved in clinical care programs.

Strengths and possibilities linked to the context

The team leader is a researcher of outstanding reputation with a clinical orientation based on the use of different human cohorts. This has led to major advances in the field of HIC. The team develops three main axes, which are led by its leader and senior permanent researchers of the team, who focus on adipose tissue and a novel immunomodulatory checkpoint (LILRB2), respectively. A plus value of this team is the access to patient samples (ANRS CO21 CODEX cohort; PRIMO cohort; OncoVIHAC cohort) and NHP models (IDMIT platform).

In collaboration with Pasteur Institute, the team leader published several advances in the field of HIC both in patients and NHP models. The team also provided additional data regarding the role of the adipose tissue in the context of viral reservoirs following their first publication in Plos Pathogens in 2015.

The team has an excellent international visibility in which the team leader is regularly invited and has published several outstanding commentaries in the HIV field. In addition, senior team members have been invited for several international congresses on HIC, the France-Japan symposium on HIV/AIDS in Tokyo in 2022 or to give a lecture in Washington on adipose tissue.

The team leader has been nominated « Chevalier des Palmes académiques ».

The team has supervised 26 internships, one post-doc, and 5 PhD over the last five years.

The team indicated a total of 255 manuscripts. As first or last authors in the HIV/SIV/SARS fields, the team has published a Cell Reports in 2020, five Front Immunol (2018, 2019, 2021 and 2022), three AIDS, JAIDS, EJI (2020), PlosOne (2018), CID (2020), Antimicrob Agents Chemother (2020), EClinicalMedicine (2021), J Antimicrob Chemother (2022), Commun Biol (2022). Furthermore, the team has published in the field of Cancer and Immunotherapy several manuscripts: three EJ Cancer, Jama Oncol, Leuk Lymphoma, Int J Hematol. Respir Med Res, Am J Hematol, and J Clin Med.

Several reviews are in major journals: Lancet HIV 2019, Nat Rev 2021, Mucosal Immunol 2022.

Furthermore, the team leader is co-author of manuscripts published with Pasteur Institute in excellent journals like Cell Metabo 2019; EMBO Rep 2020; Nat Comm 2022; JCI 2022; and Nature 2023.

Weaknesses and risks linked to the context

Whereas 49 manuscripts are related to the main axes of the team, a majority of the publications is in the fields of cancer, hepatology and autoimmunity (75 publications). Many of them are based on multiauthor papers. Independently to its leader, the impact of the papers published by the members of the team remains modest.

The team has been essentially funded by the ANRS and Sidaction during the last mandate and the resources have been limited: ANRS AC44 (96k€) and Sidaction (64k€) for projects and FRM and Sidaction for PhD salaries (146k€). The team leader is the main PI for these grants. Another senior team member has been supported by the Labex LERMIT in 2019-20 for 48 k€.

Overall, the contribution of the team to society is modest given its size and potential. Regarding the development of clinical trial, this is related to the anti-LILRB2 approach. However, this part remains limited and could be improved in the context of the new Prometheus Institute.

The team obtained a patent in 2020 on the use of anti-LILRB2. A collaboration with industry (Axenis) has led to a Cifre PhD. However, this had already been indicated in the previous report of 2013-2018.

The team has a strong links with HIV associations through Sidaction. The team, and its leader, have developed a translational research in social sciences with a team in Marseille. However, the dissemination to large audience remains limited.

Analysis of the team's trajectory

The research strategy of CoVIR will keep its focus on the mechanisms of pathogens persistence and reinforcing their research by using tissue-specific approaches in particular related to tissue microenvironment. They will pursue their strategy to combine studies both in humans and in NHP models. They will analyse the mechanisms of control of pathogens by studying T and myeloid cell subsets, in an inflammatory microenvironment, the role of cytokines (especially the role of the different interferons), as well the role of immune checkpoints and metabolic microenvironment. They will broaden their research programs to tuberculosis, S pneumoniae and respiratory viruses in the lungs. This topic fits well with the goals of IHU sepsis. Furthermore, the role of LILRsin the

mechanisms of graft rejection and CMV infection will be explored. Immunologic and virologic studies with a pharmacologic axis will be implemented to track anti-infectious and immunomodulatory drugs in blood and in tissues.

Given the size of each group within the team and the diversity of topics addressed including diverse immune cells, blood and tissues, cytokines/metabolism, and now extending the nature of pathogens assessed, there is clearly a major risk of dispersion.

Furthermore, this risk is accentuated by the new functions of its leader.

RECOMMENDATIONS TO THE TEAM

A risk for the team is related to the new function of the PI, who will be the new director of the unit, also in charge of the core facilities and deputy director of the Prometheus Institute.

A major risk is the dispersion of the topics related to the size of the team, losing at the end its international recognition. The team is encouraged to improve its capacity to be funded by European and International grants.

The team is encouraged to improve the communication between both sites, favoring PhD formation. To improve the attractiveness of the team by the recruitment of post-Doc.

Post-docs recruitment is limited.

No funding is indicated covering the next mandate.

Considering the new mandate of its leader and the dispersion of the approaches proposed as indicated above, without a clear definition of the objectives, the team is encouraged to refocus their projects.

Team 3: Auto-immune diseases

Name of the supervisor: Mr Xavier Mariette

THEMES OF THE TEAM

The LAID theme focus on pathophysiology, epidemiology, and treatment of rheumatoid arthritis (RA), Sjögren's disease (SjD), and the link between cancer and autoimmune diseases (AID).

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

1) "The team is encouraged to maintain the outstanding activities exemplary combining basic research and translational studies and the excellent quality of their scientific output. In this respect, the committee welcomes the arrival of two clinical researchers as additional strengthening of the team which is reassured to even increase its visibility at the international level."

We fully agree with the conclusion that the team are producing excellent and outstanding clinical research and we agree that these activities should be maintained. It is unclear to us if the previous examinators had any specific advice to give here. During the latest period they have also quickly acted to investigate coronavirus epidemiology, in cooperation with other teams and core facilities of the unit. An import step is that they recruited back Rami Bechara (employed 2021) who made his postdoc period in US although his work as an independent PI should be better clarified in the report. He may provide a link between the basic research and clinical applications.

2) "The committee applauds the management skills of the team leader for the fast set-up of the new FAR site research facilities. Gender balance should be actively pursued if passive processes are not working. The team could increase the number of PhD training in the future considering the number of members with HDR"

We fully agree with the suggestion to increase PhD students and it seems that this has also been done. Regarding gender balance we cannot see strong effort along this line although we would like to emphasise that it must be scientific quality which is the highest priority. Following equality guidelines could be a problem in smaller entities.

3) "The team should make a particular effort in integrating into the team project, the 2 novel research aims (Parasite diseases and HSV-1 infection)."

This advice is somewhat unclear to us but is may be a suggestion to develop closer collaborations with other teams in the unit. We think that the work on coronavirus is a beautiful example of how the different part of the unit could cooperate, which included the LAID team.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	4
Maitres de conférences et assimilés	2
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	4
Sous-total personnels permanents en activité	**11**
Enseignants-chercheurs et chercheurs non permanents et assimilés	1
Personnels d'appui non permanents	1
Post-doctorants	0
Doctorants	5
Sous-total personnels non permanents en activité	**7**
Total personnels	**18**

EVALUATION

Overall assessment of the team

The team has an outstanding scientific track record but the organisation and planning for a new generation of scientists needs to be strengthened

Strengths and possibilities linked to the context

The LAID team is very clinical oriented and has its international qualified recognition from clinical studies, both monitoring clinical studies and initiating clinical studies of already invented drugs. Based on the well-established clinical platforms the team has built strong cooperations with biopharma companies. This has resulted in both developing their science but also helping to validate pharmaceutical projects enhancing their way towards market.

The team has an excellent national and international visibility with participation in several clinical trials and cohort studies. Leader Mariette was a highly cited author in clinical Medicine by Clarivariate 2023.
The team has a continued outstanding scientific activity focused on evaluation of clinical trials in Sjögren's disease (SjD) and rheumatoid arthritis (RA). 215 papers (including 143 original papers with team members as the first author) have been published during the period. Some of these in high-profile journals (like New England J Medicine, Lancet rheumatology, JAMA and Annals of Rheumatic diseases), most in the clinical field. The number of papers during the period is an amazing achievement, however few describe original discoveries. Amongst those important discoveries one names a new mechanism of the pathogenesis of SjD with a dysregulation of salivary gland epithelial cells and the team also found a way through microRNA-liposome treatment to regulate inhibitory macrophages in the joints. The unit has outstanding core facilities, which could be used more by the LAID team for example in more basic discovery work.

The team has moved into new facilities at the hospital supported by the university. These seem to be excellent and well-equipped lab facilities.

In LAID team there are eleven scientists with permanent positions (whereof four are professors), one postdoc as well as 6 PhD students with time limited contracts. Thus, it seems that the number of PhD student has grown and the recruitment back of Bechara is a welcome additional young scientist to the team.

The team has ongoing research education with one HDR and three completed theses. Several big competitive grants has been granted and taken together, it seems that the team is well financed. During the period no patents have been filed or granted.

Weaknesses and risks linked to the context

The unit provides an excellent setting to direct research to be more discovery driven based on disease causative questions leading to identification of new targets and treatment strategies. We think these possibilities have not been used in an optimal way. We see some of their own discovery work but most are participating in various networks and help to validate projects and drugs developed by others. Most of the work with companies are on the level of assisting companies rather than building of own discoveries. The team (and unit) has the resources and know how to contribute with their own discoveries to a larger extent and this could contribute to spinout companies.

The numbers of publication are high but it should be said that many of them are based on multiauthor papers based on larger consortium studies in epidemiology or various clinical trial follow-ups, rather than discoveries originating from the team.

Team structure: The team could be organised in a more efficient way to allow and promote career of coming scientists. In particular scientist addressing fundamental questions leading to new discoveries. It is mentioned that a promising young scientist (Bechara) has been recruited but the position, independence and conditions for this person's work is not described. Our interpretation is that the team is led by the team leader (X Mariette) who is scientifically outstanding but is also the only principal investigator as judged from the publications. Planning of new recruitments should be outlined and prioritized.

Training: The reported successful PhD exams and postdocs are not as many as expected from the size of the team.

Analysis of the team's trajectory

The team has a track record of a very long term and outstanding focus on clinical research of RA and SjD. With this they have made, and make, a significant contribution. It involves organizing of clinical disease cohorts with epidemiologic analysis, analysis of laboratory and clinical parameters helping industry for validating new treatments and also initiating new treatments of already established drugs. From the self-assessment, it seems that the team is pushing forward along this line to be continuously successful.

Indeed, their contribution has been of critical value in the community during a period when these autoimmune diseases (RA and SjD) has been re-evaluated from being basically non-treatable to be treatable with efficient drugs, mainly based on the establishment of precise antibody-based treatments. Today, this is established, and the industry has a pipeline of new type of treatments for established disease. Thus, the research scope is moving towards earlier steps of the diseases and it will be important to find targets for preventive and curative treatments. The design of the unit, with well-developed core facilities with both basic and clinical research groups have a unique opportunity to fill this next step.

RECOMMENDATIONS TO THE TEAM

1) Invest in recruiting scientist with a research vision to investigate fundamental etiologic/pathogenic issues in the autoimmune disease in focus (RA and SjD), which could benefit from the established clinical expertise. This could also foster new scientific leaders within the unit.

2) Make more efficient use of the assets provided within the unit, in particular the core facilities but also to increase knowhow exchange and cooperations with other teams.

3) The team (and the unit) is very well financed, include well developed core facilities and have many permanently employed scientists. On this basis it should be possible to increase educations of PhD and postdocs. Besides fulfilling educational goal this could also strengthen the scientific goals.

4) The team (and the unit) benefit through cooperation with pharma companies through the core facilities and the clinical cohorts and expertise. This is by itself beneficial. However, the resources could also be used to a) exploit the expertise to form spin out service companies and also spin out companies based on discoveries made by the team (or by the unit).

Team 4: Hematopoietic Cells and Therapeutic Application

Name of the supervisor: Mr Emmanuel Payen

THEMES OF THE TEAM

The team is involved in the fields of stem cells, leukemia and gene and cell therapy. Thus, the main axes of the team are related to "Innovations in Gene therapy: strategies for monogenic hematopoietic and neurological diseases" and to the "Role of the bone marrow stroma and therapeutic effect of PPAR agonists in myelofibrosis and leukemia".

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous recommendations on scientific production and activities were to continue on the same trajectory that has been well pursued.

Regarding the visibility of the team at the international level, this item has not been really improved.

In term of the communications and participations to national and international meetings this item remains limited, particularly for the students. A majority of the students has a limited track record.

A JCJC has been obtained as previously recommended to reinforce the unit but the information necessary to evaluate this JCJC has not been provided.

Funding should be secured to guarantee the feasibility of the projects on the long term. The indications related to the financial supports are confused and the team will not be renewed.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	2
Maitres de conférences et assimilés	2
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	6
Personnels d'appui à la recherche	0
Sous-total personnels permanents en activité	**10**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	0
Post-doctorants	0
Doctorants	4
Sous-total personnels non permanents en activité	**4**
Total personnels	**14**

EVALUATION

Overall assessment of the team

The team's activities are in the areas of gene and cell therapy focusing on the development of a gene therapy evaluation model in Gaucher disease. They also produce new gene therapy vector for patients suffering from beta-thalassemia. The team has published in excellent journals their works demonstrating the excellence of this team.

Strengths and possibilities linked to the context

Team structure: The team is constituted by several permanent researchers including a DR Inserm, two PU-PH, and two MCU-PH. The team is member of the Carnot Opale national consortium (université Paris Saclay) and of the PASREL translational network (université Paris Saclay). Thus, a part of the research is associated with clinicians. The team has signed several partnerships with private partners, which has helped to finance part of its research programs.

A total of nine M1, 13 M2, and eight PhD students have been trained. The team has been also supported by one postdoc and three visiting researchers from Thailand and Italy. Among the eight PhD students, one failed, three have completed their thesis between 2018 and 2023, and four are currently doing their thesis. In addition to university hospital staff, some of the team's researchers give lectures in Parisian universities.

During the last period, members of the team have published 68 original publications and reviews, in which 17 publications are in either first or last author. Among the publications, the team has published manuscript in leading journals in their field including Blood, Blood Adv (x2), JCI, NEJM, Br. J. Haematol (x2), Lancet Haematol. and they are coauthors as well in several excellent journals including papers in Blood (x11), Blood Adv (4), Cell reports, Nat Med, Br. J. Haematol (x3), Hematology (x7). Thus, the team has an outstanding track record in term of publications.

Financial support from industry was obtained including in 2018 36k€ and two prestations in 2021-2024 for 281k€ and in 2022-2023 for 85 k€). Further funding included a PHRC Inter-regional in 2018 (PIO2STOP study 128 K€, NCT02889003) and an academic one in 2022-2024 60k€). They also indicated several grants from INCA (67k€), Laurette Fugain association (120 k€), foundation de l'avenir (39 k€), Cancéropole IDF (40k€), Gefluc (20k€), La ligue (23 k€) and l'institut Carnot Opale (100 k€), amongst others. A support from the French Cardiology Federation and the Healthi consortium (130k€) was obtained. A JCJC has been funded by ANR between 2018 and 2022.

The team leader is a board member of the French Society of Cell and Gene Therapy, and a member of the scientific board of the HOB doctoral school (ED561). A PU-PH is a member of the scientific and administrative committee of the French CML group (Fi-LMC), the Group For research on Adult Acute Lymphoblastic Leukemia (GRAALL) and the Acute Leukemia French Association (ALFA). He is also a member of the European Leukemia Net (ELN). He is the current president of the "Direction de la Recherche Clinique et de l'Innovation" of the "Centre Hospitalier de Versailles". Thus, he participated to the WHO2022 classification and the European Leukemia Net recommendations for CML and for ALL (2018-2024). Thus, the team and their members have demonstrated leaderships in their fields by the publication of major manuscripts and the participations in different national committees. Thus, the team as an excellent national visibility but the number of International invitations remains extremely limited.

Weaknesses and risks linked to the context

Following the team's integration into the IMVA-HB unit in 2019, two team members agreed to shift away from their historical research programs to better align the team's projects with those of the unit. This transition required time, both for securing funding and conducting experiments, but created a delay in publication.
The team has been capable to publish its research in excellent journals, although a majority of them have been published as co-authors that may not only reflect the activity of the team.

Given the numbers of M1 and M2 indicated and theses, it is of major importance and essential that several actions are required to support student communications, presentations, and publications.

Thus, regarding the size of the team and its future, a special consideration is needed regarding the students.

Analysis of the team's trajectory

The team will not be part of the future UMR. LCSAT staff will join either other teams or the core lab of the UMR1184.

Team 5: Multidrug RESISTant Gram-negative pathogens

Name of the supervisor: Mr Thierry Naas

THEMES OF THE TEAM

The ReSIST team specializes in antimicrobial resistance in Gram-negative bacteria, with a focus on beta-lactam resistance and carbapenemases. Their research encompasses the identification of novel carbapenemase-encoding genes, the structure-function analysis of these critical enzymes, and the genomic characterization of high-risk epidemic clones. Additionally, the Team investigates horizontal gene transfer mechanisms that facilitate the spread of antibiotic resistance. Beyond fundamental research, the Team also pursues translational projects for the development of rapid diagnostic tools for antibiotic resistance. In the past, the Team also played a pivotal role in SARS-CoV-2 diagnostics during the pandemic.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

1) The projects of Team 5 are appealing but ambitious with a risk of scientific dispersion. The team relies on existing collaborations that will have to be maintained and on new collaborations within the unit that have to be consolidated. Priority should be given, for the next period, to building the internal networks in order to fully integrate and support Team 5 within the new UMR1184. In addition, the Hcéres committee recommends to increase the number of HDR scientists to increase mentoring capacities of Team 5.

The ReSIST team has actively worked towards integration within UMR1184 by establishing shared research goals that engage multiple teams, exemplified by joint grant applications. Additionally, the Team is involved in the Prometheus institute research on Sepsis prevention and treatment, which will further enhance the Team capacity to tackle critical global health challenges.
The Team has also kept strengthening partnerships with diagnostic and pharmaceutical industries, as well as with national and international research groups. Particularly noteworthy is the collaboration with developing countries, focusing on antimicrobial resistance detection and advancing the One Health approach.

2) The integration of Team 5 within the new UMR1184 may disturb the team's life. It will be important to promote the integration of all team members (not just PIs) into the new unit. In the future, it would be desirable to reduce gender imbalance by recruiting women scientists.

The ReSIST team has made efforts to integrate within the UMR1184 through the application of shared grants on infection and antimicrobial resistance. This has enabled the team to access the unit's innovative research platforms and state-of-the-art equipment. At the team member level, integration and exchange remain very challenging due to the difficulties of working across two sites (Idmit and Bicetre), but unit retreats and global meetings have been organized.
Regarding gender balance, a significant number of engineers (M2 level) recruited during the reporting period were women. Additionally, one of the team members was promoted to Associate Professor in Medical Microbiology in 2022, further contributing to gender diversity within the team. Moving forward, the Team is committed to continuing its efforts to reduce the gender gap by actively promoting the recruitment of women scientists at all levels.

3) The team must persist in its opening strategy to consolidate existing projects and networks at the national and international level. In addition, the team will profit from establishing its collaborative research network within the UMR1184 to develop new projects and innovative technologies. However, Team 5 together with the UMR1184 should develop a strategy to avoid the risk of overwork. One strategy would be to reinforce the research staff either by recruiting young scientists (postdocs or PhD students) and/or full-time researchers.

The Team has addressed this comment by continuing to strengthen both national and international collaborations. They maintain close relationships with clinical laboratories, hospitals, and industrial partners, supporting their active role in public-private partnerships. At the same time, the Team also aims to develop new projects through the UMR1184 collaborative network, benefiting from advanced technological platforms.

To avoid overwork, they have reinforced their research staff by recruiting additional personnel to work on their ongoing projects. A particular example is the recruitment of a full-time researcher, Dr. Saoussen Oueslati, to support the lab's expertise in protein purification and enzymatic activity testing, which is a necessary skill for the project on structure-function analysis of carbapenemases. Furthermore, the promotion of one of the team members to Associate Professor in Medical Microbiology in 2022 has strengthened the Team's leadership and mentorship capacity.
It is unclear whether additional personnel will be recruited in the future in respect to the new collaborative projects within the other teams of the units or with the Prometheus Institute.

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

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

EVALUATION

Overall assessment of the team

The ReSIST team has achieved an outstanding level. Over the past five years, it has made significant progress in consolidating existing projects and expanding national and international collaborations. Strong partnerships with clinical laboratories and industrial partners have been established. With an exceptional publication record relative to its size, the team is now developing new projects within the UMR1184 network, leveraging advanced technologies that will further enhance its research capabilities.

Strengths and possibilities linked to the context

The ReSIST team has demonstrated an excellent ability to consolidate and expand its projects both nationally and internationally, establishing collaborations with clinical laboratories, hospitals, and industrial partners. These collaborations have enhanced the team's capacity to address global challenges, particularly antimicrobial resistance (AMR), a field requiring interdisciplinary expertise and international networks. The team's involvement in public-private partnerships further strengthens its translational research, bridging basic and applied science and enabling innovative solutions for clinical and industrial applications.

Key scientific discoveries made by the team concern the identification and characterization of novel carbapenemases and the development of diagnostic tools to detect AMR. The ReSIST team is currently composed of eleven personnel (eight "enseignants-chercheurs et assimilés" and two personnel d'appuis à la recherche et one stagiaire). The team's scientific output is notable for its size (since 2018, the team published 50 articles on scientific journals and two patents. Their publications appear in good journals (mBio, Scientific Reports, Antimicrob agents Chemother, Emerg Infection Dis, etc.), which reflects both scientific rigor and high-profile research. To elevate the team's international visibility, the team has communicated their findings at four international conferences and two posters were presented over the last 5 years. The Team PI is also involved in several international scientific organization and committees, which further reinforce international visibility.

Overall, the ReSIST team research is characterized by strong methodological and technological orientation, leveraging on their close contact with the clinic and industrial partners. Two patents result from their work on development of diagnostic tools. By accessing advanced platforms within the UMR1184 network, the team plans to pursue additional ambitious fundamental research projects, such as understanding carbapenemases spread in high-risk bacterial clones, a key focus in AMR.

Since 2018, the team has obtained seven national grants for a total of 544 k euro (as coordinators) and additional collaborative funding. The team's involvement in large-scale projects, such as the study of sepsis with funding from the Prometheus Institute (€40M), will further support their research. This last high-profile project will not only provide the necessary resources to advance sepsis research but also position the team as a leader in global health initiatives.

Internally, the ReSIST team has proactively addressed the risk of overwork, inherent in its ambitious research agenda. Recognizing the challenges of balancing workload with research goals, the team has reinforced its staff by recruiting engineers, PhD students, and promoting a member of the unit to Associate Professor in 2022, strengthening leadership and mentorship capacities.

Contribution to society is achieved through collaboration with industrial partners for the development of diagnostic tools (BForCure, NG-Biotech) and with Medecin sans Frontiers for the development of MiniLabs. The team is also actively involved in teaching at the faculty of medicine of the University Paris-Sud and the school of medicine Paris Saclay (Naas T) and participate to several teaching classes for Master students at (université Paris Diderot, université Paris Saclay. Since 2018, twelve PhD students have defended their thesis, four PhD are ongoing, six medicine/pharmacy thesis have been defended,18 Master 2 and nine Master 1, one Licence 3, 31 BTS and five high school students have been trained and five international students have been welcomed for short term stays. Since 2018, the team organizes a 2 h course for high school students (terminal S) in the frame of "les journées portes ouvertes des hôpitaux de l'APHP" and they also visit also high schools to inform students about the rise of antimicrobial resistance.

In conclusion, the ReSIST team's strengths lie in its close relation with the clinics, the ability to maintain strong national and international collaborations, exceptional scientific output relative to its size, and its integration into the UMR1184 network, which enhances technological capabilities and fosters new research directions. The team's focus on addressing critical global health challenges, such as AMR and sepsis, positions it at the forefront of infectious disease research. The combination of exceptional scientific output, interdisciplinary collaborations, and a focus on impactful global health issues ensures that the team is well-positioned for future success and innovation.

Weaknesses and risks linked to the context

The Team has proven a clear, original, and well-defined strategy to study antimicrobial resistance (AMR), with a strong focus on carbapenemases in Gram-negative bacteria, area where their expertise and contributions is widely recognized. However, the strategic approach to their work on sepsis and the microbiota is less well-articulated in the report. These broad scopes could pose a risk of scientific dispersion if the integration of diverse topics into the team's core focus. While recent recruitment of engineers and researchers has been productive, further efforts to attract senior postdoctoral scientists and candidates for permanent research positions could enhance the sustainability of these additional activities. Additionally, the significant clinical and teaching responsibilities of senior team members, combined with their research commitments, may add pressure to meet project milestones within the desired timelines.

While the team effectively leverages collaborations to access advanced technologies such as structural biology and bioinformatics, further development of in-house expertise in these areas could strengthen their capacity to advance interdisciplinary projects. Addressing these considerations will support the team's efforts to consolidate their focus and sustain their impactful contributions to AMR and infection microbiology research.

Analysis of the team's trajectory

During the evaluation period, the LReSIST team has made important contributions to antimicrobial resistance (AMR) research. Their work on carbapenemases and AMR detection has led to high-quality publications, patents, and recognition in the scientific community. Joining UMR1184 is a major opportunity, giving them access to advanced research platforms and encouraging interdisciplinary collaborations. Partnerships with biotech companies and clinical labs have also boosted the practical impact of their research, making it highly relevant to public health.

At the same time, the team's broad research scope presents challenges. While their work on carbapenemases remains focused and impactful, expanding into areas like the microbiome and sepsis risks stretching their resources that are quite limited. The team is addressing these issues by hiring engineers and researchers, which strengthens their capacity. However, to ensure long-term stability, they will need to recruit more senior scientists and secure permanent positions. This will help support their growing workload and balance the clinical and academic roles of senior members.
Overall, the LReSIST team has shown strong progress, innovation, and effective collaborations. By focusing on their core priorities and building their internal resources, they are well-prepared for future success.

RECOMMENDATIONS TO THE TEAM

To support their ambitious research, the team is encouraged to recruit more senior staff, including postdocs and full-time researchers, to expand strategic collaborations within the unit and outside. When possible, effort should be made to implement existing facilities of the Unit to include their needs or to create additional in-house facilities to support their work (-omics, imaging, etc.). This will help balance the workload and ensure continued progress.

CONDUCT OF THE INTERVIEWS

Dates

Start: 17 December 2024 at 09:00

End: 18 December 2024 at 18:00

Interview conducted: on-site or online

INTERVIEW SCHEDULE

17th December 2024

13:10	*Hcéres Rules and procedures by B. Bartosch – 10 min Public Session (all unit members)*
13:20	*Administrative and Scientific presentation of the Unit by Roger Le Grand – 30 min – 15 min questions Public Session (all unit members)*
14:05	*Hcéres Closed door meeting – 10 min*
14:25	*"Core facilities" by Thibaut Naninck, on behalf of leaders of core facilities 20 min – 15 min questions Public Session (all unit members)*
15:20	*Team 1 "Immunity and transmission" by Elisabeth Menu 20 min – 15 min questions Public Session (all unit members)*
15:55	*Hcéres Closed door meeting – 10 min*
16:15	*Team 5 "Hematopoietic Cells and Therapeutic Application" by Emmanuel Payen 20 min – 15 min questions Public Session (all unit members)*
16:50	*Team 3 "Auto-immune diseases" by Xavier Mariette 20 min – 15 min questions Public Session (all unit members)*
17:35	*Hcéres Closed-door meeting*

2nd day – 18th December 2024

9:00 T	*Team 4 "Multidrug RESISTant Gram-negative pathogens" by Thierry Naas 20 min – 15 min questions Public Session (all unit members)*
9:35	*Team 2 "Control of viral infections" by Olivier Lambotte 20 min – 15 min questions Public Session (all unit members)*
10:10	*Trajectory by Olivier Lambotte 10 min – 10 min questions Public Session (all unit members)*
10:35	*Hcéres Closed-door meeting – 15 min*
10:50 to 11:40	*Meetings with researchers*
10:50 to 11:40	*Meetings with rpost-docs/students in the absence of managing staff*
11:40 to 12:20	*Meeting with ITA (in French) in the absence of any managing staff*
	Hcéres Closed-door meeting & Lunch / meal trays;
	transfer to Faculty of medicine – Bicêtre hospital
15:00 to 15:40	*Meeting with representatives of supervising institutions; Committee – DS Hcéres – representatives of supervising institutions*
15:40 to 16:00	*Hcéres Closed-door meeting*
16:00 to 16:30	*Meeting with DU Committee - DS Hcéres – present DU (Roger Le Grand) and future DU (Olivier Lambotte)*
16:30	*Closed-door meeting of the committee and pre-writing Committee - DS Hcéres*

GENERAL OBSERVATIONS OF THE SUPERVISORS

For the attention of :

Mr Stephane Le Bouler
Acting Predident

Mrs Birke Bartosch
HCÉRES Representative

Members of the committee

Fontenay-aux-Roses, Febuary 25th 2025

Object : Evaluation report of the Unit IDMIT

N/Réf. : DIR/DRF/Jacob 2025 – 006

Dear Colleagues,

We have read with great interest the HCERES committee's report on the activities of UMR IMVA-HB/IDMIT. As the Director of the François Jacob Institute of Biology, and in the name of CEA, I would like to thank the committee for its comprehensive assessment of the unit. We particularly appreciate the constructive recommendations, which will be key to shaping the future trajectory of the UMR. We subscribe to the clarification of several key points made by the unit in response to some of the committee's critiques (namely, ERC Grant applications, Organizational Structure, Role of the Project Management Process and the Development of Advanced Models and Technologies).

Please accept, Madam, Sir, dear colleagues, our highest regards.

Pr Reiner Veitia
Director, François Jacob Institute of Biology

CEA

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EVALUATION REPORT OF THE UNIT IMVA-HB

- Immunologie des maladies virales auto-immunes, hématologiques et bactériennes-

Unit comments on committee global assessment of the unit and the trajectory

The unit thanks the committee for the valuable discussions during the oral meeting and the very comprehensive assessment report. We are particularly grateful for the constructive recommendations that will be taken into account in the development of the unit trajectory.

The purpose of this note is not to provide a point-by-point reply, but the unit considers that several points raised in the report require clarification and deserve commentary aligned with our strategic vision.

The committee was surprised that in spite of a very successful grant application activity over the last five years, no ERC grants have been obtained. This indeed represents an objective to be improved and is strategic for our next five years trajectory. The unit has significantly grown during the last period, almost doubling its capacity, the staff and the contracts in ten years. Most of the efforts were thus concentrated on consolidating our resources to sustain our development and economic model. This did not prevent the unit from recruiting several young scientists, some with high profiles and career potential for whom ERC grants would be certainly an opportunity in the coming years. We are elaborating plans at the unit and institutional level to leverage this strength. The Jacob institute and Inserm are developing individual coaching of the most promising candidates. Similar initiatives are available at the EU Office of Paris Saclay University with a dedicated support team. An expert in grant writing was also recruited by the unit in 2024.

The committee recognized the efficiency of the organization progressively developed and that we tried to continuously improve during the last ten years. However, the committee questioned the complexity of this organization and fears that a certain rigidity in planning could slow down rapid adjustments, lead to a loss of immediacy, and fragment research by limiting researchers' immersion in their projects. The unit considers, contrary to the committee's concern, that our organization was key to the very rapid adaptation of our teams to the COVID-19 research challenges, being able within a few weeks to flexibly refocus resources and expertise for preclinical and clinical priority programs. The first major results were communicated to national decision-making organizations and WHO by March and April 2020. This reactivity was the result of a highly integrated management of research teams and core facilities, with central processes to help program coordination and implementation. In particular, the unit is equipped to tackle the many constraints associated with the use of NHP preclinical models of human infectious diseases, in BSL2 and BSL3 biocontainment with highly pathogenic microorganisms, and with the ambition to integrate advanced technologies like *in vivo* whole body imaging. The unit considers that only such an organization is able to maintain a high level of competitiveness while guaranteeing European citizens the highest standard for safety management and animal welfare. This requires compliance with multiple regulatory constraints, authorizations and quality norms that are supported by the different processes and core facilities of the unit under the coordination of the

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project management process (GPE). One of the primary objectives is indeed to alleviate this heavy burden from the internal scientists and external collaborators thus promoting creative and innovative research initiatives while facilitating access to unique expertise and capacities for preclinical research in Europe.

The unit wants to clarify that the GPE does not have decision-making capacity. Instead, the GPE produces indicators to facilitate the decision-making process of the unit's direction. The GPE is a process which supports the unit management in the coordination (planning, capacity occupancy, study plans and report writing, data management and analysis, workload management, ethical GMO and CODECOH dossiers …) of the programs of both internal and external partners. The GPE makes the link between PIs and all core labs. Platform managers work with the GPE to organize the implementation of the projects by deciding on their internal organization and technological developments.

In addition to research team programs, we are cautious in promoting the research initiatives of core labs in direct interaction with basic research programs. We believe this is key to maintaining the unit at the forefront of international innovation, representing an important asset for unit attractiveness. As reported by the committee, several of the highly-cited publications of the unit with significant impact (Nature, Nature Communication, Cell…) are signed with core lab experts as main authors.

While we are aiming to develop a series of advanced technologies, animal and non-animal models and new methods, we think it is strategic to remain focused where the unit can maintain its competitiveness. In this aspect, the committee emphasizes the need to develop programs for genetic modification of mice as an important new technology area. The unit does not necessary share the vision of the committee. We are developing small animal models (HSV, trypanosome, SARS-CoV-2 and Mtb infections, for examples) and non-animal models (human lung and lymph node Precision-Cut-Tissue-Slices (PCTS) in culture, salivary gland organoids) when not easy accessible through established collaborations with expert structures and infrastructures, or when the unit considers that there is a strong positioning and differentiating approach in the field that merits significant and durable internal development. However, for most complementary expertise and approaches needed for our programs, we rely on strong established partnerships and opportunities with labs in geographic proximity. For examples, advance genetically modified and/or humanized mice models are accessible through an agreement with Institut Pasteur, and organs-on-chips platform developments are strongly supported by CEA-DRF and CEA-DRT labs to which we have easy access. We consider developing these partnerships much more efficient, maintaining access to high-level expertise, state-of-the-art facilities, and new highly innovative technologies, without dispersing unit resources across multiple new approaches, which would require investment levels that would not be sufficient to be competitive.

Unit comments on the tram-by-team or theme assessment by the committee

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In addition to points that are already included in our response to the "global assessment" of the unit, the individual teams are addressing specific comments.

Team 1: Immunity and transmission

The would like to comment on committee's recommendation "*on the need to increased translational research and clinical trials involvement".*

Our core expertise remains in fundamental research and preclinical models. These aspects will continue to be at the heart of our scientific strategy. Furthermore, we are already conducting clinical research projects, including pediatric studies on RSV infection and trials on inflammatory eye diseases. Additionally, we have identified a potential candidate vaccine for HSV-1 and Alzheimer's disease. While our basic vaccinology studies do not directly contribute to vaccine development or preclinical evaluation, they provide a foundation for vaccine discovery. We recognize the importance of strengthening the translational dimension of our research. Thanks to the involvement of our clinician colleagues within the team and the unit, we aim to expand our participation in clinical research progressively while maintaining our strong foundation in mechanistic and preclinical studies. This balanced approach will ensure that our discoveries have the potential to translate into clinical applications while preserving the high scientific standards of our work.

Team 2: Control of viral infections

The committee has recommendations on funding diversity, societal impact and risk of dispersion.

One of the recommendations was to improve the team capacity to obtain "International and European grants" since accordingly to the committee "The team has been essentially funded by the ANRS and Sidaction during the last mandate and the resources have been limited".

The origin of the funding has been diversified: ANRS and Sidaction remain an important source but we have had funds from Université Paris Saclay and from the ANR. More ambitious projects have been set up with ANR submission (adipose tissue for example). The IHU should also allow to raise more funds for collaborative studies but also for specific projects (PI). Funding do exist for the next mandate and are ongoing with 2 ANR (CLIRCOV, B Favier as PI, and AffNKill), as well as ongoing fundings by ANRS and Sidaction for the immune and clinical characterization of PLWH. A Synergy European Grant has been submitted this year and is under revision.

The committee considers that the "contribution of the team to society is modest". We dot not fully agree with this point of view. The clinical involvement of the team members is important. Although communication of our results towards media and communities could be improve, significant actions have been undertaken (oral conferences at Journées de Sidaction, convention Sidaction, and Université des jeunes chercheurs, lectures in Master and Universitary Diplomas, invitation in congress…).

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Finally, the committee pointed a" risk of dispersion", a risk which may be "accentuated by the new functions of its leader", and recommends "refocusing the research as regards to the size of the team". We would like to underline that the dynamic of the team relies on two main axis of immunoregulation: the role of interferons and the role of LILRs, with one specific domain of expertise: the adipose tissue. Three research groups are clearly identified with one PI for each: respectively N Noel, B Favier, and C Bourgeois. These groups benefit from the recruitment of new seniors for each: Leo Plaçais with N Noel, the nephrologist group with 3 seniors with B Favier and Olivier Goupille, CEA DR with C Bourgeois. The different pathogens from HIV/SIV to those involved in sepsis, allow to describe and understand the role of interferons, LILRs, and adipose tissue in different pathophysiological settings with the objective to develop immunomodulatory therapeutic strategies. The three groups work in synergy. We have to strengthen the recruitment of young people, especially post docs. The IHU is an opportunity to develop new collaborations.

The three PI are autonomous and have been working together for 10 years. The leader can rely on the CODIR of the unit and gets used to supervise different projects and programs at the same time for many years. To gain time to the team and the CODIR, he will leave the head of the Graduate School Life Sciences and Health of Paris Saclay University (70 research Units, 6 masters, …)

Team 3: Auto-immune diseases

The team would like to thank the HCERES committee for its evaluation. We greatly appreciate the recognition of our research in the field of autoimmune diseases, particularly the quality of our publications: "*Outstanding scientific activity focused on the evaluation of clinical trials in Sjögren's disease (SjD) and rheumatoid arthritis (RA). 215 papers (including 143 original papers with team members as first authors) have been published during the period", as well as the acknowledgment of Xavier Mariette as a highly cited researcher.*

We would like to take this opportunity to clarify a few points and respond to aspects of the evaluation that may have been perceived as weaknesses:

1- Limited interaction with the "animal model" platforms

First, we would like to highlight that during the previous five-year period, our team conducted a study aimed at developing a non-human primate (NHP) model of RA through immunization with citrullinated peptides. These findings were presented during the evaluation. This model presented a nice immune response specific of citrullinated peptides, but the NHP did not develop polyarthritis. Thus, even if the model gave new interesting insights about genetics of RA (very well published in the top 1 Rheumatology journal), it did not recapitulate the disease and was therefore abandoned.

Additionally, the team has worked on murine models of RA, particularly the CIA model. Looking ahead, we plan to develop new murine models of SjD, including spontaneous models (NOD-H10), induced models (such as immunization with salivary protein extracts or with the Ro60 (SSA) antigen), and models with targeted gene deletions in epithelial cells using the Cre-Lox system. This work is fully

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integrated into the unit's core facility and will be a key project in the upcoming five-year period, enabling in-depth mechanistic studies. Finally, considering the societal challenges surrounding animal models, our team is also working on establishing non-animal preclinical models (organoids) in line with the 3R (Replacement, Reduction, Refinement) approach.

2- Results based on larger consortium studies in epidemiology or various clinical trial follow-ups, rather than discoveries originating from the team

We respectfully disagree with the evaluators. First, to progress in clinical and translational research, we effectively need collaborations and consortia. It is what we have done in SjD by building and coordinating the French ASSESS cohort and the European NECESSITY consortium. It is thanks to these consortia that we have made the following new discoveries: 1) The new predictive markers of lymphoma in SjD (rheumatoid factor and activity of the disease); 2) The interest of treating low grade lymphoma in the context of SjD; 3) The different clusters with different evolution of patients with SjD; 4) The new composite score of evaluation of the SjD: STAR

We now plan to set-up collaborative groups for studying the effect of new immune therapies like CAR-T cells and bispecific antibodies in autoimmune diseases.

Second, our work in the lab has led to new potentially important discoveries in the past 5 years: 1) The cross-talk between epithelial cells and immune cells in SjD, firstly by 2D culture and now by developing immuno-organoids, which could become one of the best ex-vivo models of the disease; 2) The defect of m6A methylation of RNA (epitranscriptomics) for dampening inflammation in epithelial cells, and which could explain accumulation of dsRNA in the cell and thus the interferon signature in autoimmune diseases. It is a completely new concept in autoimmune diseases that could have therapeutic consequences; 3) In RA, the specific defect of polarization of monocytes in anti-inflammatory macrophages and the ability in mouse models of improving the disease by correcting this defect; 4) The effect of JAK inhibitors of the activation of NK cells, which could explain why these drugs could have a negative effect on cancer immunosurveillance

3- Most of the work with companies are on the level of assisting companies rather than building of own discoveries. The team (and unit) has the resources and know how to contribute with their own discoveries to a larger extent and this could contribute to spinout companies. It is true that, until now, we have not created start-up or spinout companies. This could be an objective for the future. However, our strength is the access to the patients and a large knowledge and expertise of all the mechanisms potentially involved in autoimmune diseases. Creating start-up takes a lot of time, requires complementary expertise and, frequently, avoids embracing new fascinating news areas of research. We assume the fact that our role is rather to explore new domains of autoimmunity pathophysiology that could be exploited later by other for developing drugs or for proposing management protocols for a better safety of new drugs leading to an improvement of the quality of care. Just a few examples:

- At the time where we began to highlight the role of B cells in autoimmune diseases, 25 years ago in 2000, very few people were believers of B cells and now, we may perhaps cure some autoimmune diseases with anti-CD19 CAR-T cells

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- We were the first to have published in 2003 the role of the BAFF cytokine for activating the B cells in SjD and now, we have drugs inhibiting BAFF or BAFF-R available for the patients in SjD and lupus

- We were also the first in 2006 to demonstrate that BAFF was induced by interferon and thus, to suggest the role of the IFN signature in the activation of autoimmune B cells

- Thanks to our research on registries and cohorts of patients with RA treated with biologics, we have allowed improvement of the safety of these drugs and, particularly, participated to the demonstration that anti-TNF could be given safely to patients with antecedent of cancer.

4- The organisation and planning for a new generation of scientists needs to be strengthened. A promising young scientist (Bechara) has been recruited but the position, independence and conditions for this person's work is not described. The reported successful PhD exams and postdocs are not as many as expected from the size of the team. Again, we respectfully disagree with evaluators. Among the 5 PI of the team, 3 have been recruited during the past 5 years with a high liberty of scientific development: 1) Rami Bechara has got a permanent position at Paris-Saclay University and was hired with the objective to develop the thematic of epitranscriptomic in autoimmune diseases in a total liberty; 2) Audrey Paoletti has got a permanent position at INSERM and is the PI for developing the work on macrophages in RA and autoimmune diseases; 3) Samuel Bitoun was hired as assistant professor and is going to develop the topic of new depleting B-cell agents in autoimmune diseases. 4) Each of these three Pi has got her/his own funding. Last, the deputy leader of the team, Gaétane Nocturne will succeed to Xavier Mariette for leading the team in 2027.

Regarding the number of PhD and post-docs, we supervised during the past 5 years 7 PhD and3 post-doc, which is in relation with the size of the team. This increase will continue in the upcoming period, with two new HDR (Habilitation à Diriger des Recherches) accreditations planned in the coming months (Rami Bechara and Samuel Bitoun), further strengthening our supervisory capacity.

Team 4: Hematopoietic Cells and Therapeutic Application

The committee main comment was on the absence of publications for one of the team members since 2020. Following the team's integration into the IMVA-HB unit in 2019, two team members agreed to shift away from their historical research programs to better align the team's projects with those of the unit. This transition required time, both for securing funding and conducting experiments, which explains the delay in publication.

Team 5: Multidrug RESISTant Gram-negative pathogens

The committee first commented that « ReSIST has few or no common publications with the other teams of the UMR." Team LResist was hospital based until August 2022, when the they moved to the new

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research building, allowing to implement closer interactions with the other Bicetre-located teams, especially CoviR and LAID. Since several projects have been deposited for funding. In addition, LResist was a founding member of the IHU Promotheus on Sepsis, which will allow to develop several new projects based on bacterial specificities and the corresponding host responses with different teams of the Unit. These collaborations will lead to the development of novel diagnostic tools and therapies such immune therapies.

The committee also questioned the teams' trajectory : "ReSIST team has made important contributions to antimicrobial resistance research with high-quality publications, patents, and recognition in the scientific community. Partnerships with biotech companies and clinical labs have also boosted the practical impact of the team's research. While their core project on carbapenemases will remain impactful, expanding into areas like the microbiome and sepsis risks stretching the team's resources too thin and will require recruitment of permanent senior researchers. To support their ambitious research, the team is encouraged to recruit more senior staff, including postdocs and full-time researchers, to expand strategic collaborations within the unit and outside. When possible, effort should be made to implement existing facilities of the Unit to include their needs or to create additional in-house facilities to support their work (-omics, imaging, etc.). This will help balance the workload and ensure continued progress."

The team considers a recruitment of an Inserm permanent researcher and post-doctoral candidates. While recent recruitment of engineers and researchers has been productive, further efforts to attract senior postdoctoral scientists and candidates for permanent research positions could enhance the sustainability of these additional activities. Additionally, the significant clinical and teaching responsibilities of senior team members, combined with their research commitments, may add pressure to meet project milestones within the desired timelines. Nevertheless, we are a small team, and yet we managed to be highly productive on our core activity, while initiating novel projects that led already to several publications (Nature comm, Lancet Microbes).

La tutelle, Université Paris-Saclay, n’émet pas de réponse institutionnelle de type « Observations de portée générale ».

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