Research evaluation

EVALUATION REPORT OF THE UNIT
Unité de biologie des infections

UNDER THE SUPERVISION OF THE FOLLOWING ESTABLISHMENTS AND ORGANISMS:
Institut Pasteur Paris,
Institut national de la santé et de la recherche médicale – Inserm

EVALUATION CAMPAIGN 2023-2024
GROUP D

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High Council for evaluation of research and highter education

In the name of the expert committee[1]

Alain Filloux, Chairman of the committee

For the Hcéres[2]

Stéphane Le Bouler, acting president

Pursuant to Articles R. 114-15 and R. 114-10 of the French Research Code, evaluation reports drawn up by 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 Alain Filloux, Nanyang Technological University Singapour
Experts:	Ms Priscille Brodin, Institut Pasteur Lille Ms Catherine Schuster, Institut national de la santé et de la recherche médicale, Strasbourg Mr François Vandenesch, Université Claude Bernard Lyon Ms Christine Chatellard, Institut de Biologie Structurale, Grenoble

HCÉRES REPRESENTATIVE

Ms Anne Marie Di Guilmi

REPRESENTATIVES OF SUPERVISING INSTITUTIONS AND BODIES

Ms Patricia Renesto, INSERM, Institut thématique Immunologie inflamma microbiologie
Mr Patrick Trieu-Cot. Institut Pasteur

CHARACTERISATION OF THE UNIT

- Name: Biology of Infection Unit
- Acronym: BIU
- Label and number: U1117
- Composition of the executive team: Marc Lecuit

SCIENTIFIC PANELS OF THE UNIT

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

THEMES OF THE UNIT

This is a single team unit whose research work is mostly dedicated to understanding key aspects of infectious diseases and the arm's race between the host and the pathogen. The unit used Listeria monocytogenes (Lm) as the main model organism, which is a bacterial pathogen associated with food poisoning and which leads to death in 30 to 45% of the cases. This includes identifying clinical/microbiological features of this bacterial species isolated from human listeriosis, as well as using mice models to determine features relating to the invasion mode and the host response during infection. The unit is thus at the interface between cellular and clinical microbiology. Another research direction for the unit is not necessarily the most prominent theme but involves a sound expertise of the director and of members of the unit. It is associated with a number of collaborations and aims at the study of viral diseases, including emerging threats like SARS-Cov-2, Zika, Chikungunya or encephalitis viruses. Although these two topics may look distant and unrelated to be conducted within a single team, the expertise converges in the ability of these organisms to be associated with maternal fetal and central nervous system infections.

Overall, the research themes are fully relevant to help control and prevent emergent diseases which may have a significant impact on human health and well-being in the years to come.

HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

This single unit team was established in 2013 as a follow-up from a previous five-year Institut Pasteur and avenir-Inserm group (2008–2012) led by the director of unit. It is solely based at the Institut Pasteur and still supported by both Pasteur and Inserm as supervisory institutions.
In addition to the director, the unit includes three PIs, two from Inserm and one clinician (APHP, 20%). Of note the director is also a specialist in infectious diseases at the Necker-Enfants Malades hospital and is the director of the national reference laboratory for listeriosis. The unit BIU manpower in 2022 is 16.7 FTE including 4 PIs, 4 Post docs, 6 assistants, technicians or engineers, 4 PhDs and one Master student.

The combination of basic scientists and clinicians helps to develop a multidisciplinary approach to study the mechanisms of host infections.

RESEARCH ENVIRONMENT OF THE UNIT

The unit is affiliated to the Department of Cell Biology and Infection, of which the unit director was also the chair (2019–2023) and benefits of the scientific and technical environment of the Institut Pasteur. It is hosted in recently renovated laboratories and is very well equipped. The unit possesses in house light and confocal microscopes as well as a flow cytometer which helps on supporting cellular microbiology research and delivering on the scientific objectives. In addition, the unit benefit of the formal collaboration Institut Pasteur has with other French research institutions (e.g. CNRS, Inserm…) as well as formal cooperation agreement with Universités in Paris, and notably Université Paris Cité (UPC). UPC and Pasteur are members of an IDEX (Initiative d'Excellence) since 2022, which thus benefits the unit to secure doctoral contracts. This single team unit is affiliated to two Doctoral schools, ED 562 (BioSPC, Biologie Sorbonne Paris Cité) and ED 474 (FIRE, Frontières de l'Innovation en Recherche et Éducation). The unit is also involved in structure created by the PIA (Programme Investissements d'Avenir) and member of the LabEx Integrative Biology of Emerging Infectious Diseases (IBEID) headed by Philippe Bastin and Carla Saleh, involving about 60 PIs. In this context the unit obtained several funding for PostDocs, PhDs and various scientific programmes including on Zika research. As many other Institut Pasteur teams, the unit is also part of the Institut called INCEPTION for the study of emergent pathologies. The unit has also been part of many Institut Pasteur transversal projects studying the role of the microbiota in health and diseases. Overall this highly collaborative environment has led to major scientific publications.

The unit Director is also leading the South-East Asia encephalitis project, which involves teams in Laos (mostly UK-led, Oxford and Wellcome Trust), Necker and Institut Pasteur Cambodge. The unit is also associated with the Institut Carnot Pasteur Microbes & Santé, which supports translational research. Finally, the director of the unit is the head of the Listeria National Reference Center, while the connection with the IHU Imagine (Necker Enfants-Malades) helps connectivity and links with clinicians at AP-HP. In this context the director is a member of the steering committee of the CEREDIH (Centre de référence des Déficits Immunitaires Héréditaires).

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

Catégories de personnel	Effectifs
Professeurs et assimilés	2
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	4
Sous-total personnels permanents en activité	**8**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	0
Post-doctorants	1
Doctorants	4
Sous-total personnels non permanents en activité	**5**
Total personnels	**13**

DISTRIBUTION OF THE UNIT'S PERMANENTS BY EMPLOYER: in physical persons at 31/12/2022. Non-tutorship employers are grouped under the heading 'others'.

Nom de l'employeur	EC	C	PAR
INST PASTEUR PARIS	0	0	3
AUTRE	2	2	1
Total personnels	2	2	4

GLOBAL ASSESSMENT

This unit is a single team based at the Institut Pasteur, as well as institutionally supported by Inserm, and led by an internationally renowned scientist in the field of *Listeria monocytogenes* (Lm) pathogenesis and emergent viruses. The main research theme is on Lm, but the integration of the emergent virus research is built around an expertise on CNS and placental infections and the development of preclinical models. The concept of Lm as a studied organism model applicable to other diseases is very strong and appropriate. It allows to solidly anchor the unit research into the study of detailed mechanisms of action of Lm pathogenesis processes.

The outstanding research of the unit is then reflected into an exceptional level of publications, both in terms of quality and quantity (when considering the size of the unit). This is also consistent with the level of external funding secured, among which the most internationally recognised awards such as ERC starting and consolidator grant. Very little doubt that the unit director has the talent and capability to go one step further with an ERC advanced grant.

Despite a deep desire to unravel mechanistic aspects, the unit is also profoundly associated with clinical research, the unit director himself being a clinician. This has led to the assembly of a unique cohort of patients with Listeriosis (MONALISA, Cochin Hospital, 1700 patients enrolled), while the unit director is also the director for the National Reference Centre for Listeria. A recent initiative also led by the director stems in South-East Asia and is based on a large cohort to study children viral encephalitis. This led to the identification of Japanese encephalitis virus and enterovirus as leading cause of encephalitis in children, the latter shares with Lm a tropism for the Central Nervous System and the maternal-fetal unit. Resources and interface with the hospital are ideal to address problems of major importance in infectious diseases, which is clearly timely considering the example of recent pandemics and emerging/re-emerging diseases. There are also clear opportunities for the unit to engage translational research and this is done through various supports including the Carnot network or direct partnership with companies (e.g. PROSION therapeutics).

The unit is driven by the strong, inspiring, energetic and charismatic leadership of the director. There is a clear adhesion to the unit project by all unit members and at all levels from researchers, technicians, postdocs and students. The director leads most of the grant applications but there is room for other scientists to contribute and

to secure grants like ANR and ANR JCJC. Some will also have opportunities to develop their own project (e.g. ageing).

The project is sound and ambitious and would contribute to put Institut Pasteur and French research on the map of infectious disease research. The level of ambition is reflected by high-profile publications which sometime may take longer than the duration of a PhD project to be published. The training is, however, excellent and the destination of post-docs/PhDs also rather successful, some being recruited back into the unit as researchers (CR Inserm) or engineers. The team has a rather small size but adequate to conduct the research planned, especially when including the national and international collaborations involved. The research theme on viruses has been weakened by the sad passing away of one of the team researchers in 2022, and the committee would like to convey all its sympathy to the director and the unit members for their loss.

DETAILED EVALUATION OF THE UNIT

A – CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

One main recommendation in the previous report was to integrate better the sub aims to increase synergy and cohesion of the research plan.

This has been partly addressed by combining in vitro, ex vivo and in vivo models of infections, with epidemiologic and genomic approaches, resulting in a nicely multidisciplinary programs leading to publication in journal with impact in medicine and basic science such as Lancet Infectious Diseases, J Exp Med, Science Advances, Nature communications and Nature. All of them are with the unit director as lead author and two include study groups.

The other main recommendation was about the flaviviruses and other arboviruses research direction, which is out of the mainline of research of the team.

This has also been addressed by indicating that this research axis makes use of the unit expertise in viral infections and the associated collaborations, which again led to groundbreaking publications in journals like Nature Neuroscience, Nature, Science, Science translational medicine and Nature communications. Whereas most of these publications do not have the unit director as lead author, they could have not been conducted independently of the unit, whose input is instrumental. Furthermore, it seems clear the director is a prominent scientist in the field being invited to international conferences in the field of emerging viruses and part of global networks (e.g. Global virus network, Arbo-France network). Considering the importance of this field of research, it is worth for the unit to continue along these research lines.

B – EVALUATION AREAS

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

Assessment on the scientific objectives of the unit

The scientific objectives of the BIU unit are outstanding. The objectives are based on what has been built since 2008, namely the study of molecular mechanisms involved in infectious processes using a large set of relevant models of bacterial and viral infections. They combine basic and transdisciplinary research to cover medical unmet needs, which is clearly outstanding. The Unit has a two-decade recognised expertise in the field of Listeriosis. The Unit benefits from an outstanding institutional environment and brings contributions on numerous collaborations on emerging viral diseases.

Assessment on the unit's resources

The unit resources are outstanding considering the relatively small size of the unit given the restrictions on staff maximum number imposed by the Institut Pasteur. The unit is supported by recurring funds by two host Institutions, Inserm and Institut Pasteur. Inserm contributed to personnel support with the recruitment of one permanent researcher and one half-time engineer during the period. Institut Pasteur hosts the unit and contributes with state-of-the-art equipment and favoured access to dedicated platforms for in vitro and for in vivo work on transgenic animal models of infection. Institut Pasteur also contributed to personnel support with the recruitment of one half-time engineer, one half-time assistant and a full-time technician during the period. The unit secured numerous grants from national bodies ANR, FRM and internal calls as well as from the ERC.

Assessment on the Functioning of the unit

The functioning of the unit is outstanding, benefiting from the combined support of its two host institutions. It adheres to the Institut Pasteur's guidelines for human resources management strategy in research (HRS4R), utilises scientific data storage servers from the Institut Pasteur to collect and organise large sets of genomics, transcriptomics and imaging data. The Unit prioritises environmental awareness, and implements a continuity plan (PCA).

1/ The unit has set itself relevant scientific objectives.

Strengths and possibilities linked to the context

The BIU unit is perfectly positioned for the studies of host-pathogen interactions from bench to bedside through its unique links between the Institut Pasteur, Inserm and the Hospital environment. The objectives fit within the scientific strategy of the host institutions Institut Pasteur and Inserm. The unit head is recognised worldwide for its research on Listeriosis. The models developed for Listeria are subsequently used for emerging viral infections, which is remarkable. The small team is capable of conducting research on multiple subjects with brio. The tight link with the Listeria CNR (Centre National de Reference) and the clinics is also a major asset for continuing tackling the next emerging human infections.

Weaknesses and risks linked to the context

None

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

Strengths and possibilities linked to the context

The unit localisation within the Institut Pasteur enables the access to massive technological and methodological expertise ranging from cell biology, state-of-the-art microscopy, microfluidics, 3D culture system, animal models, bioinformatics support. Equipment is available either within the Unit (Inverted confocal Zeiss LSM710; Upright Airyscan Zeiss, Lightsheet Zeiss and BD Biosciences LSR Fortessa) or at dedicated platforms. The unit resources are outstanding with a combination of sound recurrent funding and personnel support from both institutions Institut Pasteur and Inserm and as recipient of major national and international funds.

Weaknesses and risks linked to the context

The costs to access the animal facilities are around 60 k€ per quarter, which is far below from what the Unit receives of recurrent funding (on average 110 k€).

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 unit fully complies with the rules of the Institut Pasteur in terms of human resources management and data management, which follow the principles of the European rules. Among the permanent personnel, six are women (four engineers/technicians, two researchers), the two men are researchers.

The personnel in the unit, for all categories, reported to appreciate the tailored management of the unit head. The management of the CNR and the clinical activities of the PI appears to be well balanced with that of the research activity since he could benefit from some clinic duty reduction.

Weaknesses and risks linked to the context

None

EVALUATION AREA 2: ATTRACTIVENESS

Assessment on the attractiveness of the unit

Attractivity is outstanding. Scientific reputation is highlighted by outstanding publications, invitations worldwide and remarkable capacity to raise funds including ERC and ANR grants as leader or partner. The unit successfully integrates fundamental, translational and clinical research and benefits from an outstanding scientific, clinical and technological ecosystem. Reputation is further supported by unique bacterial strain collections and preclinical models. Strong appeal is demonstrated by the capacity to attract talented postdocs and PhD candidates as well as highly gifted support personnel.

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

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

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

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

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

The unit is worldwide renowned as a leader in the field of Listeria monocytogenes and virus-host interactions, due to the high quality of the scientific outcome with several outstanding publications in the field and the remarkable capacity to drive cross-fertilisation of fundamental, translational and clinical research projects. Collaborations outside the main field of interest (i.e. emerging viruses) have also given excellent publications with national and international partners.

The collaboration network of the unit at the national (Inserm, Saint-Louis, Paris) and international (Liège, Belgium) level is constituted of leading scientists and institutes in the field (the team leader is the coordinator of the South-East Asia Encephalitis international project including partners from Cambodia, Vietnam, Laos, Myanmar). As a recognition of their scientific expertise, the unit was part of several Pasteur transversal projects, focused on microbiota, brain cognitivity and neurodegenerative diseases, emerging infectious diseases, antimicrobial resistance, microbes and pain, as well as the Labex IBEID, the institut Convergence INCEPTION, the Institut Carnot 'Microbes et Santé'.

Unit members were invited over the period to give more than 100 seminars as invited guests in prestigious universities and centers (MacGill, Montreal, Canada; Umea University Sweden; Doherty Institute seminar, Melbourne, Australia; Yang Ming University, Tapei, Taiwan; Biozentrum, Basel, Switzerland, Imperial College London, Trinity College Dublin, Ireland; WHO headquarters, Geneva, Switzerland) as well as keynote conferences in important events of the field (e.g. World Science Forum, Dead See, Jordan, 2017; Netherlands Centre for One Health Annual Scientific Meeting, Rotterdam, Netherlands, 2018; American Society of Microbiology (ASM), San Francisco 2019, Washington 2022, USA; International Symposium on Listeria, Seville, Spain, 2020; 39th RICAI, Interdisciplinary Meeting on Antimicrobial Therapy, Paris, France, 2019; 48th Annual Meeting & International Symposium of the Korean Society for Microbiology and Biotechnology, Busan, South Korea, 2021).

The team leader was an organiser in 2019 of the 20th International Symposium on Problems of Listeria and Listeriosis (ISOPOL), Toronto, ON, Canada, and was in charge over the period of the organisation of the seminars of the Cell Biology and Infection (BCI) Department of Institute Pasteur.

Unit members take part in scientific international councils (ERC starting grant, Human Frontiers Science Program) and national (Fondation Bettencourt Schueller, Fondation pour la Recherche Médicale), Scientific Advisory Boards (RHU Torino-Lumiere, Ecole Nationale Vétérinaire d'Alfort, Oncobiome Consortium, AVIESAN I3M), they are members of scientific societies (EMBO Global Investigator Committee, American Association for the Advancement of Science, American Society for Microbiology, American Society for Cell Biology, European Society for Immunodeficiencies) and co-chair of the Institut Pasteur Global Virus Network Excellence Center.

Unit members act on editorial boards (Member of Faculty of 1000 Biology, Section Microbiology Frontiers in Cellular and Infection Microbiology, Journal of Visualised Experiments, F1000 research, Virulence, Microbial Pathogenesis), and participate in reviewing for prestigious journals (Nature, Science, Nature Medicine, Lancet infectious Diseases, PNAS, New England Journal of Medicine).

The team leader is the director of the Listeria National Reference Center and the WHO collaborative Centre, building the world biggest collection of Lm strains (MONALISA project). The unit has also developed precious mice models to mimic human Lm infection. The unit leader is renown as a key opinion leader in the field, he was Director of the Biology and Infection Department at Institut Pasteur over the period. The unit director got national prizes (Prix Duquesne, Prix Eloi Collery, Académie Nationale de Médecine Prix Zermati) and was awarded Member of Academia Europae, EMBO Member, ESCMID Fellow, and IUF Senior Member.

The unit hosted eight postdocs, 7 PhDs (Switzerland, Paris, Rennes) and thirteen Master-level students (Ecole Normale Supérieure, Université Paris Diderot, Semmelweis University Hungary, Université Rennes, Sorbonne University, Paris Cité Université, Upsala University Sweden) during the period. The unit hired as well technical staff members with high expertise in microscopy and cytometry. All members benefit from the hosting policy framed by the Institute Pasteur in terms of gender equality and promotion of women in science. Over the period the unit recruited one CR and two IR (all women) on tenured positions. Scientists are encouraged to apply to calls to gain their own funding. All members, including support personnel contribute to publications. The unit hosted eleven visiting scientists coming from the Institute Pasteur worldwide network (Marocco, Tunis, Senegal) and from foreign universities or institutions (Costa Rica, Spain, Poland, Taiwan).

The funding capacity is outstanding with external resources (>1 M€ per year) obtained as coordinator from the European Council (ERC consolidator grant Invadis, Zik Alliance (partner), Fonds National Suisse, EMBO), from competitive national calls as coordinator (3ANR SEAEe, MUCOLIST, MONALISA, 1ANR JCJC ORGANOLIST, 1CRC AP-HP) and as partner (2 ANR LIVALIFE, CHICKHOST), from PIA (5 IDEID Labex, 1 ANR inception), as well as from charities (FRM, AFM…). The ERC consolidator grant Invadis aims to investigate the microbial invasion and dissemination within the host, the mechanisms and the effects. The ANR MonaLisa Genbio concerns the genetic susceptibility and markers in listeriosis and is coordinated by a clinician scientist in the unit. The JCJC ANR ORGANOLIST, led by a team member present in the unit since 2008, is about the interactions of Listeria monocytogenes with the intestinal epithelium.

The unit benefits from the state-of-the-art platforms of the Institute Pasteur, and participate actively in the advisory core facility councils for these equipments. The main equipment bought by the unit over the period are three microscopes and one cytometer.

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

The majority of the funding, scientific visibility and PhD supervision is in the hands of the PI although as mentioned above, team members were successful in raising funds.
All PhD candidates co-authored publications but have not signed as first or co-first author. This is mainly due to the nature of the projects which are long-term and ambitious and may fall short being published over the PhD period. Two postdocs (out of 8) were not successful in terms of publications.

EVALUATION AREA 3: SCIENTIFIC PRODUCTION

Assessment on the scientific production of the unit

The scientific production is outstanding with more than 100 peer-reviewed articles among which the record for the main area of research is remarkable in both quantitative and qualitative terms. Production of the unit in translational research and in collaboration is also notable.

1/ The scientific production of the unit meets quality criteria.

2/ The unit's scientific production is proportionate to its research potential and properly shared out between its personnel.

3/ The scientific production of the unit complies with the principles of research integrity, ethics and open science. It complies with the directives applicable in this field.

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

The Unit's scientific output in its main area of research, the pathophysiology of Listeria infections, is remarkable in both quantitative and qualitative terms, with a significant number of publications in prestigious journals such as Nature (1 PDC), Science (1 PDC), Science Advances (1 PDC), Nature Com (2 PDC), Nature Microbiol (1 PDC), Nature Neuroscience (1 PDC), JCI (1 PDC). In addition to these fundamental publications, there is also a significant translational or clinical output related to the unit's themes, for example: J Infect (2 PDC), Lancet Global Health (1 PDC), Lancet Child and adolescent health (1 PDC), Lancet Infect Dis (1 PDC), Clin Infect Dis (4 PDC), Clin Microb Infect (3 PDC), Emerg Infect Dis (1 PDC). This medical valence reflects the clinical anchoring of this unit, two of whose researchers (including the team leader) are university hospital teaching researchers (PU-PH). The unit director is also director of the National Reference Centre for Listeria. The team's strategy of using its experience of neuromeningeal infection to study viral pathogens with neuromeningeal tropism has been particularly productive on Zika (Nature Neuroscience (1 PDC), Nature Microbiol (1 PDC editorial), not to mention the articles published in collaboration with other teams on Chikungunya (Nature, 1 penultimate author), COVID-19 (Science Transl Med, 1 penultimate author), Zika (JCI, 1 penultimate author) among others.

Given the size of the unit, the scientific output appears to be particularly abundant, well above the usual standards in terms of both quality and quantity. As expected, given that the main holder of research contracts is the team leader, the latter is pre-eminent in the position of last author (except in collaborative works). Other researchers and PhD students are well represented in the articles, with postdocs and engineers regularly signing

as first author; although only one PhD student has been awarded first authorship in a major journal (Hafner et al, Nat com 2021), which, however, is in accordance with the policy of the unit that targets ambitious projects, challenging research questions and high-quality publications ('quality over quantity').

The unit has benefited from the Institut Pasteur's deployment of an electronic laboratory notebook, the main functions of which are traceability, individual authentication of contributions, completeness, security and archiving of data. Accessibility and interoperability make it possible to work together in accordance with best practice. Institut Pasteur also provides access to various data storage and management tools and infrastructures, as well as to specific software supplied by the institution (REDSao, OWEY data lake, etc.).

On the question of predatory journals and conferences, the report clearly states their policy. The scientific record illustrates their strategy and demonstrates a very clear desire to privilege almost exclusively prestigious traditional journals (Nature, Science, Lancet, etc.) or those affiliated with learned societies (Clin Infect Dis, Clin Microbiol Infect, etc.).

In terms of open science, almost all of the unit's publications are available on HAL (Hyper Article en Ligne); and in terms of data traceability, conservation and accessibility, a very convincing data management plan is presented in the report.

In terms of respect for human and animal life, the ad hoc systems and services for research on humans and for animal experimentation are explained in the report; they seem to be well integrated into the unit's policy.

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

The only point to watch out for is the publications of PhD students, who do not often occupy significant positions in terms of authorship.

EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

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

Outstanding for the interaction with the non-academic world and public health bodies as well as for sharing the research with the general public. Excellent considering the links with the socio-economic world

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 team started to successfully interact with the private sector to work on innovative compounds that reduce the rejection of transplanted organs. The unit contracted an industrial partnership (PROSION Therapeutics) beside their scientific research program, to test products predicted to inhibit actin tail polymerisation by *L. monocytogenes*.

Its active engagement in the Carnot network has resulted in securing funding for the advancement of applied research, with a subsequent focus on transferring the developed technology. The team has also obtained funding from FRM (Fondation pour la Recherche Médicale) to supplement PhD students' grants.

Moreover, a patent titled 'Anellovirus Genome Quantification as a Biomarker of Immune Suppression,' which was filed several years ago, has been licensed to Biomerieux since 2020. This innovative diagnostic test enables the evaluation of immunosuppression levels in patients, facilitating the customisation of treatment according to the observed pathology (cancer, chronic infection, organ transplant…).

The team leader, who is the director of the Listeria National Reference Center and the WHO collaborative Centre, built the world biggest collection of Lm strains (MONALISA project).

Additionally, his involvement in clinical research at IHU Imagine (Necker Enfants-Malades) strengthens connections with AP-HP clinicians. Using these established connections with AP-HP opens significant opportunities for advancing translational research projects.

These patents, coupled with strategic partnerships formed with companies, underscore the considerable economic significance of these research activities in addressing crucial public health issues.

The team leader took part in outreach activities: lesson at the Collège de France in 2018, participation in the production of a practical booklet on food microbes for the general public. Team members are also involved in various popular activities such as hosting of several high school students 'collège and lycée', taking part in 'Fête de la Science' and also communicating research news through social media. Several members of the unit are regularly in contact with students through classes at the university and at Pasteur Institute.

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

Fewer economic developments (patents, clinical tests, etc.) were initiated during this period.

ANALYSIS OF THE UNIT'S TRAJECTORY

The scientific directions of the unit will not change in the next five years. The main focus remains most essentially on the study of Listeria, together with emergent viruses which, as Listeria, can cross host barriers and are associated with maternal-fetal and CNS infections.

The research has in the past mandate been very successful and published in high-profile journals both in basic science and medical fields. These publications clearly indicate how the unit has been able to deliver on its five main objectives which were:

i) Lm translocation across the intestinal barrier,
ii) impact of microbial port of entry (e.g. Goblet cells) on microbial fate,
iii) molecular basis of Lm hypervirulence,
iv) predisposition to invasive infections (MONALISA cohort)
v) and neuro-invasive emerging viruses, including Chikungunya, Zika and SARS-CoV-2.

The next mandate will further address questions on the mechanistic, evolutionary and epidemiological/ecological aspects of these infections, and is split in four major questions. These are:

i) in depth understanding of the Lm-Host interactions,
ii) virulence factors involved in Lm transmission,
iii) evolution of the Listeria genus in response to adaptation to host and environment,
iv) and mechanisms of maternal-fetal and CNS infections associated to emerging viruses.

Listeria has always been a flagship of Institut Pasteur research, and the proposed and very detailed plan presented suggests that there are still major breakthroughs to be found, while the unit remains the world leader in this research field. In this unique context, the programme is multidisciplinary and integrates in vitro, ex vivo, and in vivo models, clinical cohorts, together with state-of-the-art genomics and cellular biology approaches.

In aim i), few original and novel questions are, to address the role of the gut microbiota in resistance or promotion to Lm carriage, to decipher how Lm may evade immune responses in a mucus-dependent manner, to develop imaging of real time infection using Zebra fish as model, to understand how microglial cells respond to Lm invasion (adult or neonatal brain), to study Lm invasion of the placenta and dissemination to the fetal tissues using models and human placental explants, and to use single immune cell analysis to understand the increased age susceptibility to Lm infections, combining infection models and patients data as well as identifying other host-factor susceptibility using GWAS data from the MONALISA cohort.

In aim ii) the main novelties are to consider differential expression of virulence genes in Lm to explain clinical prevalence and to use the zebra fish model and mathematical modelling to monitor the flow of barcoded Lm through the organs and the role of various virulence factors.

In aim iii) one of the hallmark is to use 80K Listeria genomes to trace the evolution of virulence traits and host adaptation since geological times and understand the phylogeography of the genus to trace the spread of major clinical strains.

Finally, aim iv) is far less documented and rather vague on the specific objectives. It will study emerging virus and has incorporated one more virus, enterovirus 71, which seems to be the focus of the next mandate as part of the SEAe project led by the unit director.

Overall, this is a very ambitious program, although very comprehensive and attractive, and relies on a limited manpower, although involving collaborations. Several of the subprojects are involving at most a PhD student and a technician. The project on Listeria evolution will involve a Postdoc bioinformatician still to be recruited and might require far more expertise to be advanced smoothly. Even though several new grant applications are in the pipeline or planned (e.g. ERCAdG by the unit director), the delivery on all objectives remains speculative while the core research has to be based on available resources.

RECOMMENDATIONS TO THE UNIT

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

The size of the unit is adequate to conduct the ambitious project planned but this will be eased by strengthening the recruitment rate of technical and researcher personnel. It will be appropriate to engage discussion with both supervising bodies on this matter. In terms of Institut Pasteur personnel, there is a full-time technician, a half-time engineer and a half-time assistant in the unit and one of the researchers sadly passed away in 2022. She was involved in research on emerging viruses and her replacement would further strengthen this important research direction. As for technical staff, the unit has only benefited over the past fifteen years of a 50% part-time Inserm engineer position since 2022, and it would be timely and appropriate to convert that position into a full time one.

The research director shows a remarkable energy and delivers at high level despite being multitasked, including fulfilling his clinical duties. It will likely be justified and of great benefit to recruit a project manager and this discussion could also be engaged with the institutions. Such category of personnel could also be included in large grant applications such as an ERC advanced grant.

The unit has a limited number of researchers and all should be encouraged to obtain their HDR so that the number of PhD students enrolled could further be increased.

The pre-clinical work is hugely costly, and it should be carefully considered on how this could be supported through external grants and institutional supports.

Recommendations regarding the Evaluation Area 2: Attractiveness

It is important to nurture and promote the emergence/visibility of talents and expertise within the unit. This should naturally be inspired by the energy the director insufflates into this team. There are researchers that could be encouraged to grow their independence, and there are also highly qualified research engineers that could be further recognised and rewarded for their exceptional and long-standing contribution to the unit.

The level of funding is quite superb, including ERC consolidator grant obtained by the unit director. It is recommended, although surely already considered, to apply for an ERC advanced grant as well as for an 'Equipe FRM'.

Recommendations regarding Evaluation Area 3: Scientific Production

The committee can only recommend that the outstanding research is continued.

Although it is clear that an ambitious and high-profile project like the one describes for the unit takes time, especially for delivering high-profile publications, a good balance in short-mid and long-term objectives could be carefully considered so that all PhD students obtained 1st author publication in the best appropriate timeframe.

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

The unit should continue to develop and encourage the cross-talk between fundamental research and medical activity, as well as to increasingly consider translational/integrative approaches.

There is an excellent connection with the hospital, a good number of MDs, and clinically relevant work could also be further connected to the CNR Listeria, which is also headed by the unit's director.

The unit should exploit the vision of a charismatic and opinion leader, namely the unit's director, to convey key messages in the field of infectious diseases, and strengthen its visibility across the public, caritative associations or patient's association.

CONDUCT OF THE INTERVIEWS

Date(s)

Start: 01 février 2024 à 8 h

End: 01 février 2024 à 19 h

Interview conducted: online

INTERVIEW SCHEDULE

Session publique (comité + membres de l'unité + direction + tutelles)

7 h 30 **Déroulé de la visite HCERES.** Anne Marie Di Guilmi
7 h 30 – 7 h 40 **Présentation des membres du comité.** Alain Filloux
7 h 45 – 8 h 15 **Présentation des activités de l'unité.** Marc Lecuit
15 min présentation + 15 min discussion
Présentation des projets en cours. *10 min présentation + 15 min discussion*
8 h 20 – 8 h 45 Hana Kammoun
8 h 50 – 9 h 15 Claire Maudet
9 h 20 – 9 h 45 Sylvain Levallois
9 h 45 – 10 h **Pause**
10 h 5 – 10 h 35 **Présentation de la trajectoire.** Marc Lecuit
15 min présentation + 15 min discussion
10 h 35 – 11 h 15 **Discussion interne comité**
11 h 15 – 11 h 45 **Réunion avec personnel chercheurs et enseignants-chercheurs**
11 h 50 – 12 h 20 **Réunion avec personnel ITA**
12 h 30 -13 h 00 **Déjeuner**
13 h – 13 h 30 **Réunion avec étudiants et post-docs**
13 h 30 – 14 h 15 **Discussion interne comité**
14 h 15 – 14 h 45 **Réunion avec les représentants des tutelles**
14 h 50 – 15 h 20 **Réunion avec la direction de l'unité**
15 h 30 – 17 h **Finalisation rapport**
17 h **Fin de la visite**

PARTICULAR POINT TO BE MENTIONED

None

GENERAL OBSERVATIONS OF THE SUPERVISORS

Unité de Biologie des Infections
Inserm U1117

Paris, le 30 mars 2024

To the HCERES Committee

Dear President,
Dear Committee Members,

The members of the Biology of Infection Unit would like to thank the members of the committee for their interest in our work and for their very positive and encouraging assessment of our achievements and projects. We are happy and grateful that our unit was considered outstanding in all areas evaluated.

We have made some suggestions for minor corrections in the report.

We also thank the committee for their helpful recommendations.

The entire unit is truly grateful to the entire committee for the time you spent evaluating our research, for the quality and usefulness of your report, and for your helpful and stimulating feedback.

Sincerely,

Marc LECUIT, MD PhD

Biology of Infection Unit
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