

EVALUATION REPORT OF THE UNIT
UPIV - Unité de Pathogénèse des infections
vasculaires

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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In the name of the expert committee:

Alain Filloux, Chairman

For the Hcéres:

Stéphane Le Bouler, acting president

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

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

Chairman: Mr Alain Filloux. Nanyang Technological University Singapour

Experts: Mme Priscille Brodin. Centre d'Infection et d'Immunité, Lille
Mr Paul Verhoeven. CHU, Saint-Etienne; CIRI, Lyon
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Mme Patricia Renesto. ITMO 3M, INSERM
Mr Patrick Trieu-Cot. Institut Pasteur
Mr Didier Mazel. Institut Pasteur

CHARACTERISATION OF THE UNIT

- Nom : Unité de Pathogénèse des infections vasculaires
- Acronyme : UPIV
- Label et numéro : U1225
- Composition de l'équipe de direction : M. Guillaume Duménil

SCIENTIFIC PANELS OF THE UNIT

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

THEMES OF THE UNIT

The focus of the unit is to investigate infections in the context of blood vessels. This is a highly original and unique objective, which involves a multidisciplinary approach.

Initially the concept was to study many different pathogens, including bacteria, viruses, or parasites, but in fact the work and effort are concentrated on one bacterial pathogen which is *Neisseria meningitidis*. This bacterium is human adapted and there are no animal models available. The unit has thus developed a unique grafting of human skin on a mouse which allows the coupling of mouse blood circulation to human vessels. Furthermore, the unit has also developed an *in vitro* model based on microfluidics and which allows to reconstitute the mechanical confinement of the bacteria within a vessel, and the impact it may have on behaviour including gene expression.

The research questions are thus concentrated around the interaction between the bacterium and the vessels/endothelium. They can be split into few main axes which are:

- i) role of the type IV pili in attachment and colonisation,
- ii) bacterial response and adaptation to the confinement of vessels,
- iii) modification of the host environment to colonisation, including protrusion, cytoskeleton reorganisation and membrane deformation,
- iv) importance of neutrophils and immune escape strategy.

Overall, this is a very concise strategy, highly relevant in the context of infectious diseases and antibiotic resistance, and which could potentially be adapted to other pathogens involved in vascular infections.

The approaches are truly multidisciplinary and going from structural biology, notably cryo-EM, to cell biology, immunology while involving clinical research with patient cohorts, and translational research with antimicrobial drug design.

HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

This is a single team unit (UPIV, Pathogenesis of Vascular Infections) which originates from a team ATIP-Avenir to the current director and created in 2009. The team was originally based at the Paris Research Centre Cardiovascular (PARCC), before moving to Institute Pasteur in 2015 where it became a unit in 2019. It is located within the Department of Cell Biology and Infection, which is also headed by the unit director.

The unit is rather small (15 persons) but involves two recently recruited CR Inserm (2019 and 2022). These two researchers defended their HDR in 2023 and the unit already involved three Ph D students and one Postdoc. One researcher (DR Inserm) committed at 20% and involved in immunological studies is based in Strasbourg (IBMC).

RESEARCH ENVIRONMENT OF THE UNIT

The unit is affiliated to the Department of Cell Biology and Infection of which the current director is the chair since 2023. The unit thus benefits of all available platforms (e.g. Ultrastructural Bio-Imaging, UBI) and infrastructure at Institute Pasteur, including connections through the Labex IBEID (Integrative Biology of Emerging Infectious Diseases) or the DARRI (Direction des Applications de la Recherche et des Relations Industrielles) Carnot Institute. The unit also benefits from the link between Institute Pasteur and University Paris City and the associated IDEX (since 2022), thus benefiting of potential doctoral contracts. The unit is also affiliated to another doctoral school, which is ED562 BioSpC.

The unit is also involved in clinical research and benefits of a collaboration with a PU-PH at the Henri Mondor hospital in Creteil. This provides access to cohorts of patients suffering from meningococcal diseases.

There is also a good spread of technical expertise across the researchers and the technical staff. The Inserm researchers are experts in biophysics and innate immunology, while a research engineer is specialised in vascular biology, a technician in molecular biology or an assistant engineer.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	2
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	5
Sous-total personnels permanents en activité	9
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	0
Post-doctorants	4
Doctorants	3
Sous-total personnels non permanents en activité	7
Total personnels	16

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

Nom de l'employeur	EC	C	PAR
AUTRES	0	4	2
INST PASTEUR PARIS	0	0	3
Total personnels	0	4	5

GLOBAL ASSESSMENT

This is a Pasteur Institute-based unit made of a single team. The head of the unit has an outstanding track record in *Neisseria* research. He is a world renowned scientist for his work on type IV pili, which he has now connected into the broader study of *Neisseria meningitidis* pathogenesis notably in the context of sepsis and meningitis. This research includes the study of *N. meningitidis* behaviour in the constraint space of vessels. This is a very specific scientific niche, and the models and technologies used to address these questions are unique to this unit and seen as a hallmark in the *Neisseria* and type IV pili scientific communities.

The publications output and momentum are quite exceptional, and notably the quality of the papers that have for example been published in influential journals like Nature Communications, Nature Methods, Cell, PNAS or yet EMBO J. This type of output naturally gives the team international exposure and competitiveness to secure major funding, which has been the case through ANR, including JCJC, ERC advanced or ERC starting grants.

The research is at the forefront of basic science and at the same time the implications in terms of therapeutic applications are very significant. This mindset and desire to establish the unit at the interface between basic/clinical research is a concept well established within the unit, although deliverables in translational research are not necessarily expected to be short- or mid-term outcomes. The unit has connection with hospital (e.g. Henri Mondor hospital) can enrol cohort of patients, including from Low and Middle-Income Countries (LMIC) through collaboration with the international network of the Pasteur Institute, has opportunities to engage with industrial partners (e.g. Sanofi-Aventis) and can get support from the Carnot Institute to carry on with translational project and the identification of new therapeutics.

The momentum of this single team unit relies on the leadership of the director but also on the two other researchers with Inserm positions, who have provided substantial input in designing projects ultimately supported by prestigious grants (ANR JCJC or ERC). This combination of talents provides an attractive multidisciplinary environment, encompassing basic microbiology to immunology and using sophisticated and innovative in vitro/in vivo models. Each scientist provides excellent mentorship to the cohorts of PhD students (4) and post docs (3) and nurture the career development of these younger scientists.

In all, the project has multiple facets, that is

- i) structure functions of Neisserial virulence determinants,
- ii) physiology and fate of the bacteria in a confined context (e.g. vessels),
- iii) role of perivascular macrophages in vascular infections
- iv) or impact of infections in the context of tissues.

It is appropriately ambitious, and benefits of the superb infrastructure of the Pasteur Institute to allow research within this multidisciplinary dimension, including using the cryo-electron microscopy facility.

DETAILED EVALUATION OF THE UNIT

A – CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

In the previous report the one recommendation was to secure funding beyond the expiration of the ERC Consolidator grant awarded to the unit director. This has been addressed through the unit director securing an ERC advanced grant which started in 2023, which is a remarkable achievement, as well as now having the label 'equipe FRM'. The other researchers in the unit are also playing a significant role in securing funding since one researcher has obtained a grant from ANR JCJC. What is not mentioned in the report is the fact that one young researcher obtained an ERC Starting Grant in 2023 for the HOMEPATH project.

B – EVALUATION AREAS

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

Assessment on the scientific objectives of the unit

The scientific objectives of the unit are outstanding. In the continuation of the work accomplished in the last ten years, the team objectives focus on the understanding of the basic cellular mechanisms involved in bacteria-mediated sepsis and meningitis. A combination of cleverly designed humanised tissue models and state-of-the-art mechano biology, microfluidics and dedicated imaging tools are used. The team has established its niche in the mechanobiology of infections, with an excellent positioning in relation to international competition and has clearly the means to achieve its scientific objectives.

Assessment on the unit's resources

The resources are outstanding considering the relatively small size of the Unit. The Unit is supported by recurring funds by two host Institutions, Inserm and Institut Pasteur. Inserm contributed to strong personnel support with the recruitment two permanent researchers and one engineer during the period. Institut Pasteur in Paris hosts the Unit in a brand-new building equipped with state-of-the-art platforms dedicated to imaging, microfluidics and mechanobiology. The team has access to facilities and has established a unique model of human skin grafted on pre-clinical model combined with intravital microscopy, which is really outstanding.

Assessment on the functioning of the unit

The functioning of the Unit is excellent considering the complementary support of the two host institutions. The Unit follows the rules of the Institut Pasteur in terms of human resources management strategy for research (HRS4R), of scientific data storage servers managed by the DSI (Direction des systèmes de l'information), of animal ethics, of environment awareness and continuity plan (plan de continuité d'activité, PCA). Of note, the HRS4R appears to be fully in line with those from Inserm, that is the main employer of most researchers from the Unit.

1/ The unit has set itself relevant scientific objectives.

Strengths and possibilities linked to the context

The main scientific objective is the study of the pathogenesis of *Neisseria meningitidis* (or meningococcus) to better understand two extreme forms of the diseases: sepsis and meningitidis. The research falls into 4 axes:

- 1) the structural biology of the main bacterial virulence factors, Type IV Pili;
- 2) the interaction of bacteria with host cells;
- 3) the impact of infection on blood vessel function
- 4) and the role of the innate immune system.

The Unit has a proven outstanding publication track and there is no doubt this will continue.

The scientific project is perfectly mastered by the UPIV members and associates all the necessary interdisciplinary skills starting from tissue biology, cellular microbiology up to imaging and physics. With its localisation at the Institut Pasteur, the unit benefits from the best national environment to address a multidisciplinary approach involving pathogenic bacteria and cellular models of infection and imaging equipment including state-of-the-art intravital microscopy.

The recent recruitment of two permanent young researchers with expertise in biophysics and innate immunology are strong assets to achieve the multidisciplinary objectives.

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 presents a recognised expertise in the field of mechanobiology for the understanding of bacterial-host interactions. It is perfectly integrated in the scientific landscape of the Pasteur Institute department of Biology of Infections, with the Unit head being now the Department Head.

In terms of human resources, the small size of the Unit makes it very reactive. It is composed of personnel affiliated either to Inserm or to the Pasteur Institute. During the reporting period, the Unit was able to recruit two permanent researchers at Inserm and the Unit will continue to recruit contractual researchers in the next contract given the prestigious grants that has been recently secured. There are currently sixteen persons in the Unit. UPIV hosts four permanent full-time researchers, four PAR, welcomed six postdoctoral fellows and trained 6 doctoral students. The number of PAR allows for optimum management of the numerous equipment and facilities used in the Unit. Indeed, the Unit has access to state-of-the-art equipment for instance for intravital imaging, microfluidics

devices and as well as to the Pasteur Institute platforms such as the facilities, the Imagopole and the mass spectrometry platform. Of note, the Unit collaborates with many Pasteurian Units, for instance the one on image analysis. These resources are key to the success of the projects based on the permanent development of innovative technologies applied on tissue models for the deciphering of the molecular mechanism of bacterial invasion. The Unit benefits also from the access of the PPU program that allows the recruitment of international PhD students of high level.

Weaknesses and risks linked to the context

None

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

UPIV predominantly hosts ten men and 6 women, with a man as Unit director. With regards to PhD students and postdoctoral fellows, there is a full parity (50%).

UPIV complies with the Pasteur Institute rules that has released a Gender Equality Plan (GEP) in January 2022. In the unit more specifically, the director has followed training on unconscious gender bias and makes sure to apply them in the management of the lab.

The Unit is very sensitive to the promotion of their female collaborators, in particular one of the new researchers recruited is a woman. A great deal of autonomy is given in order to help them build the new recruited scientific career with the obtention of their own grants.

The Unit complies with the Pasteur Institute requirements to ensure protection of the nation's scientific and technical potential. As such, scientific data is backed up on servers managed directly by the Institut Pasteur.

The members of the Unit are involved in animal experiments. Of note, the personnel are involved in committees taking care of animal well-being.

UPIV being located at the heart of the French capital and takes measures to minimise its impact on the environment. The Unit is vigilant on four issues:

- 1) restrict water consumption,
- 2) carbon accounting,
- 3) reduce purchase with the Ressourcerie
- 4) and garden deployment.

Weaknesses and risks linked to the context

The Principal Investigator has initiated efforts by establishing working groups aimed at enhancing collaboration within the Unit.

Careful consideration is needed to facilitate the growth of a newly awarded team under the ERC Starting Grant while safeguarding the outstanding multidisciplinary expertise of the current PI's team.

EVALUATION AREA 2: ATTRACTIVENESS

Assessment on the attractiveness of the unit

The attractiveness of the unit is outstanding through the Principal Investigator's visibility and scientific reputation. The Principal investigator actively facilitated the development of talented researchers recently recruited, thereby elevating the unit's attractiveness and solidifying its academic reputation.

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 funding capacity of the unit is excellent with external resources (mean of 530 k€/year) representing more than 80% of the total annual resources. The unit was successful with competitive national grants as coordinator (1 ANR, 1 ANR JCJC, NRJ/Institut de France) or partner (2 ANR), for a total amount of 790 k€. Contracts were obtained by the unit as partner, one from PIA (Labex IBEID) and one from the Institut de Convergence (Inception). Four contracts coordinated by the unit were financed by socio-economic partners (Bayer, UPSA) and four others also coordinated by the unit were raised through charities like FRM.

The unit is highly involved in national and international meetings (>25) including Keystone symposium, Gordon Research Conference, ECCMID conference, ASCB Annual Meeting and in national steering bodies (PI is member of CSS5 INSERM).

Over the period, the unit showed a solid record of recruitment with of three PhD students recruited as well as 6 post-docs researchers including two who obtained a CRCN Inserm position in 2019 and 2022 demonstrating its competitive position.

The attractiveness of the unit for senior researcher is high: a DR Inserm, team leader from IBMC Strasbourg, worked part-time in the unit. He brings a complementary expertise in innate immunity. The unit also hosted a visiting professor from Seoul National University in Korea for a sabbatical. In addition, all members benefit from the Pasteur Institute career development center.

The quality of staff management policy is outstanding with members encouraged to follow trainings and to move forward in their careers. All unit members benefit of a personal integration and career monitoring. Post-docs have been recruited and supported for getting independent fundings to become independent researchers or group leaders.

The unit attractiveness for the quality of its major equipment and technological skills is excellent. In addition to the excellence of Pasteur institute core facilities, the unit has developed innovative tools to monitor infections. This included high-tech imaging technics to perform cutting edge intravital imaging microscopy and long-term dynamic imaging of infected pre-clinical models. In addition, the unit has developed biochemical tools such as chromatography protein purification systems (AKTA purified) to purify proteins and complexes.

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

No weaknesses identified

EVALUATION AREA 3: SCIENTIFIC PRODUCTION

Assessment on the scientific production of the unit

In summary, the scientific productions by the team led by Guillaume Duménil demonstrate innovation, significance, and broad interest across various fields within the biology of infections. The quality of research works is outstanding and the publication of these findings in prestigious journals reflects their quality and impact within the scientific community.

- 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 scientific productions of the team led by Guillaume Duménil demonstrate a robust interdisciplinary approach, combining molecular biology, microbiology, biophysics, and bioinformatics to address fundamental questions in infection biology and cellular physiology.

Their work not only advances our understanding of microbial pathogenesis and host-pathogen interactions but also contributes valuable tools and methodologies for the broader scientific community.

The publication of their work in prestigious journals underscores its quality and impact within the scientific community.

The team has published five original articles directly addressing their research question. The team members are found in leading position in all these publications and the unit leader (Guillaume Duménil) is corresponding and last author in all these publications. As for example, the team has published two articles in *Nature communications*, one article in *PNAS*, one article in *EMBO* and one article in *Cell*:

1. Colonization of dermal arterioles by *Neisseria meningitidis*: This work gives new insights about the pathogenesis of *Neisseria meningitidis*. This study sheds light on the intricate interactions between pathogens and host tissues, providing new insights into how *Neisseria meningitidis* establishes a niche within dermal arterioles to evade of the host immune response. This work published in *Nature communications* in 2021 involved several team members and was led by a PhD student graduate in 2018 and supervised by the PI.
2. Inhibitors of the *Neisseria meningitidis* PilF ATPase: This study elucidates the pivotal role of type IV pili in bacterial pathogenesis and identifies a new therapeutic strategy for combating *Neisseria meningitidis* infections. This work published in *PNAS* in 2019 involved 6 team members including the first author and the PI as corresponding and last author.
3. Deep Mutational Scanning of the *Neisseria Meningitidis* major Pilin: By employing deep mutational scanning techniques, this research provides insights into the functional importance of pilus tip-mediated adhesion in *Neisseria meningitidis* pathogenesis. This work was published in *EMBO Journal* in 2019 with a PhD student as the first author, another PhD student as the second author and supervised by the PI.
4. Adhesion to nanofibers drives cell membrane remodelling through one-dimensional wetting: This study elucidates how *Neisseria meningitidis* manipulate cellular membranes to facilitate infection. The authors introduce 'one-dimensional wetting' as a new mechanism governing cellular interactions at the nanoscale, which is exploited by meningococci during infection. This work was published in *Nature communications* in 2018 in the context of a PhD thesis who signed as first author this article.
5. Intermittent Pili-Mediated Forces Fluidize *Neisseria meningitidis* Aggregates: This study elucidates the biomechanical principles underlying bacterial aggregation and vascular colonisation, providing novel insights into the interplay between bacterial adhesion, aggregation dynamics, and host tissue remodelling. This work was published in *Cell* in 2018 was led by a postdoc fellow, currently CR in the team and awarded of an ERC starting grant.

In addition, the team contributed to three original articles published in collaboration with different teams. In these three papers, team members have made various levels of contributions but were not in the first or last position. Overall, collaborations appear to be well established, and publications in collaboration with other teams are excellent:

1. TrackMate 7: The integration of segmentation algorithms into tracking pipelines is crucial for advancing biological research involving dynamic processes, such as cell migration or protein trafficking. The UPIV team contributed to this excellent collaborative paper published in *Nature Methods* in 2022. This work was supervised by the head of the Image Analysis Hub at the Institut Pasteur. The contribution of several members of the UPIV to this work highlights the team's interest in infection dynamics.
2. Advanced *in vivo* Cross-Linking Mass Spectrometry Platform: Such methodologies are invaluable for elucidating the complex networks of protein interactions underlying cellular processes and disease mechanisms. Two members of the team contributed to this original article published in the journal *Analytical Chemistry* in 2021. The team members are well ranked in this collaborative work, a postdoctoral fellow in the UPIV team (from 2017 to 2021) in 3rd position and the Guillaume Duménil as second-last Author.
3. SARS-CoV-2 infection induces the dedifferentiation of multiciliated cells: This research contributes to our understanding of the pathogenesis of COVID-19 by revealing the impact of SARS-CoV-2 infection on respiratory epithelial cells. Guillaume Duménil took part to this work published in *Nature communications* in 2019.

The recently graduated PhD students have produced excellent original articles. They all done outstanding research works that are directly related to the question addressed by the team. Findings are published in prestigious journals including EMBO Journal, *Nature communications*.

The team has also published literature reviews and editorial materials:

1. The Many Faces of Bacterium-Endothelium Interactions during Systemic Infections: This review synthesises current knowledge on the complex interactions between bacteria and endothelial cells during systemic infections, highlighting the diverse strategies employed by pathogens to subvert host defences and promote dissemination. This review was published in *Microbiology spectrum* in 2019 by a CR and Guillaume Duménil.
2. Short review published in *Trends in Microbiology* in 2019 was published by Guillaume Duménil.
3. A literature review in French was published by several members of the team in 'Comptes Rendus Biologies' in 2020
4. Guillaume Duménil was editor of a Book of the series *Advances in Experimental Medicine and Biology* untitled 'Physical Microbiology' published in 2020.

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

The team's auto-evaluation highlighted the irregular nature of its scientific production. We also note that PhD students do not publish literature reviews. By encouraging PhD students to publish high-quality literature review, the team could strengthen its scientific production. Two post-docs were not able to publish their research during the mandate because they were hired early by a prestigious university in Japan and a major pharmaceutical company, which highlights the excellent international visibility of the team.

EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

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

The overall assessment of the unit is excellent. Over the course of the mandate, the unit has increased relevant actions to communicate on their research activities. The unit devotes 10% of its activity to administration and animation of research, 10% for scientific mediation and sharing knowledge with the general public and 10% for the valorisation and innovation.

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

This unit promotes high-level translational research by applying its findings in the clinical context. To this end, they have participated in a first multicenter prospective clinical study involving four intensive care units (publication in 2013). A second clinical study is currently underway in collaboration with the intensive care unit at Henri Mondor hospital in Creteil, focusing specifically on meningococcal infections. Resources from value-adding, transfer and industrial collaboration represent between €25,000 and €30,000 for 2021 and 2022 respectively. Non-academic partnerships cover the development of new therapeutic approaches, for example, in collaboration with Sanofi-Aventis (Toulouse). This project involves close collaboration with chemists at the University of Leiden (Netherlands). To develop this DARRI-Carnot project, the team has obtained joint funding from the Institut Carnot and the Institut Pasteur (140 k€). B. Marteyn has raised funds from Bayer (€27,600) and UPSA (€9200) for the period 2020–2023, which enabled a clinical study (VITAL) to be carried out within the international network of Pasteur Institutes (Bangui, Nouméa). The unit has also been awarded ANR funding 'Science with and for Society' in 2021 to communicate about the research carried out at the Pasteur Institute, in collaboration with the communications department. The target audience is mainly students of all ages but also the broad public.

The valorisation of the research results enabled the team members to file a patent in 2011 in which methods developed to screen substances that could be used for the prevention and treatment of Neisseria bacterial infections were described. Even if no development on this patent is carried out, the laboratory is nevertheless continuing its strategy of developing therapeutic tools (inhibitors, nanobodies...).

G. Dumenil also acts as a consultant to the scientific committee of the biopharmaceutical company GlaxoSmithKline (GSK) France, for the medico-economic modelling of vaccination against invasive meningococcal infections.

The unit mainly uses the Pasteur Institute website to communicate about its scientific results. On this site, each team has its own dedicated page. Publications are available in English, but some are also in French. The team has produced videos of their participation to international conferences. They have also created videos in French for students in collaboration with the French Ministry of Education (Corpus). Those videos are visible on the Pasteur Institute website.

The unit carries out actions to promote communication with non-specialised audiences to help them to better understand and recognise their research projects, such as in 2022 at the town hall in the 15th arrondissement of Paris (information found on the Pasteur Institute website). One of the team's researchers is involved in transmitting knowledge of research processes and professions to high school students through two different programs (Declics and L'Oréal-UNESCO 'Pour Les Filles et La Science').

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

The unit has developed a unique highly innovative *in vivo* intra-vital imaging pre-clinical model (grafted with human skin) to study meningococcal infection. It would be interesting to communicate about this tool to develop collaborations with clinicians (bacteriologists/infectiologists) and/or industrial partners.

ANALYSIS OF THE UNIT'S TRAJECTORY

The research trajectory of the unit does not include major changes as compared to previous objectives. It essentially aims at capitalising on the recent discoveries and the development of new models which include the humanised pre-clinical model and the microfluidic devices resulting in mechanically confined bacteria as they would be in vessels.

The multidisciplinary approach remains and expand towards cryo-electron tomography to visualise type IV pilus growing inside bacterial cells.

The objective is also to expand on translational approach, in particular Type IV pilus as therapeutic target, exploiting the identification of inhibitors of the PilF ATPase for further drug design as well as furthering the structure of the pilus to understand immune escape strategy.

Note that there are many more groups working on T4P and it will be interesting to understand how this research, notably the structural work is inserted into the larger scientific community.

One major development will also exploit the observation that *N. meningitidis* in the mice model as well as in the confined environment becomes highly resistant to antibiotics, although this is not acquired resistance. This is rather contextual and is worth investigating in far more depth. This is the main research objective which has been proposed in the ERC advanced grant obtained by the director in 2023. This project is called DESTOP – Destabilising vascular colonisation to stop meningitis – and holds great promises.

The other main approach is understanding the interaction of the bacteria and the host cells and tissues, as well as the interplay with the immune system. This involves the mechanical response of the host to the contact with the bacteria, notably the T4P. The approaches to unravel this complex dialog are also multidisciplinary, although some of the experimental design and research questions are a bit vaguer.

RECOMMENDATIONS TO THE UNIT

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

The unit is articulated around three PIs, the director (DR Inserm) and two other scientists (CR Inserm) with expertise in biophysics and immunology. It would have been appropriate to encourage the two CRs to obtain their HDR, but this has now been completed in 2023. This is working extremely well but is also a rather fragile organisation. The reason is that the two young scientists are extremely talented and would rightly look for independence in the years to come through independent funding (ANR JCJC or ERC starting grant). Whereas the director can only be congratulated for nurturing scientific talents, he should also anticipate on maintaining a sufficient task force within the unit. The committee can thus only encourage the director to engage/continue discussion with Inserm and Pasteur Institute so that the best possible arrangement could be made to retain the most promising staff within the unit or anticipate new recruitment.

The innovative aspects of the methods used in the unit also call on experts' technical staff. It is advised that care be made in anticipating the needs to maintain technical skills. One technician in charge of all bacterial genetics is approaching retirement. A research engineer with all the expertise in intravital imaging may have far more demands for projects than he could take. Another technician with electron microscopy expertise has recently joined the unit but his future prospective seems unclear. Finally, one technician instrumental to the development of animal models is a 50% Inserm position, sheared with another unit at Pasteur Institute. Although, and for the moment, this pool of technicians covers all the need of the unit, the committee is concerned about the sustainability of such organisation and here also will encourage that the director engages discussion with Inserm and Pasteur Institute to anticipate future recruitment or replacements.

The reason for the success of the unit also relies on the originality and multidisciplinary aspect of the research projects and on the models used, including pre-clinical models. Likely for this reason major grants have been secured over the years. Yet it would be advisable to encourage the unit to develop further, and whenever appropriate, interactions with the broader French scientific community working on *Neisseria*, which is quite significant nowadays.

The mentoring from each PI seems to be very careful and effective, but through discussion with the PhDs and Post Docs, the committee felt that there may be a need for more cohesion across the projects and particularly when it comes to share technological expertise. This could likely be addressed through continuing to increase the communication and discussion between the director and all categories of personnel, so that any issues be do not remain silent and is addressed.

Besides the three PIs based at Pasteur Institute, the unit is also involving a 4th PIs, previously at Pasteur Institute and now at 80% based at the IBMC in Strasbourg. The complementarity and expertise in immunology, and notably neutrophil research, provided by this scientist appears to this committee of great value. One can only encourage that this translates into publications with co-authorships, which has not been the case so far.

Recommendations regarding the Evaluation Area 2: Attractiveness

The funding obtained by the unit is quite exceptional, and it is a rare thing to see that in such a small unit one PI secured an ERC advanced grant whereas another was awarded an ERC starting grant.

These grants not only bring further international visibility but also provide opportunities to develop new projects and identify new objectives, like the impact of vessels confinement on *Neisseria* antibiotic resistance, and this should be properly articulated and integrated in the future unit's project.

Recommendations regarding Evaluation Area 3: Scientific production

The committee can only encourage the team to continue publishing in high-profile journals, as it has been the case so far. There are many papers that are currently in preparation. It is important to keep a regular and steady output, even though it is understandable that the finalisation of ambitious and complex projects may take longer.

A couple of post docs have not published during the period, but it is because they have been attracted to other more permanent positions. This suggests that the unit should be vigilant and make plans on how to retain talent and not loose expertise. It is also important to follow closely the timing for preparing papers with key authorship for PhD students and Post Docs.

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

The UPIV team has developed a very innovative in vivo infection model combined with live intravital microscopy that will enable breakthrough discovery, and open perspectives to translate the findings into clinical research. Pushing the interface between basic and clinical research is thus very much within the remit of the unit and should be encouraged further.

In other words, while the UPIV team carries exceptional basic research, it has a great potential to bring its outstanding expertise to the bedside to contribute to accelerating the development of efficient therapeutic strategies (antimicrobials, vaccines, nanobodies). With this in mind, the team should have the potential to promote bench to bedside research by bringing together researchers with medical doctors involved in the care of patients with meningitidis.

CONDUCT OF THE INTERVIEWS

DATE

Start: 07 mars 2024 à 8 h

End : 07 mars 2024 à 19 h

Interview conduct : online

INTERVIEW SCHEDULE

8 h Déroulé de la visite HCERES

8 h – 8 h 20 Réunion avec personnel ITA

8 h 25 – 8 h 45 Réunion avec personnel chercheurs et enseignants-chercheurs

8 h 50 – 9 h 10 Réunion avec étudiants et post-docs

9 h 10 – 9 h 30 Discussion interne comité

9 h 30 – 10 h Pause

10 h – 10 h 55 Présentation des activités de l'unité, bilan et trajectoire.

11 h – 11 h 30 Réunion avec les représentants des tutelles

11 h 30 – 12 h Discussion interne comité

12 h – 12 h 30 Réunion avec la direction de l'unité

12 h 30 – 13 h Déjeuner

13 h – 15 h Finalisation rapport

PARTICULAR POINT TO BE MENTIONED

None

GENERAL OBSERVATIONS OF THE SUPERVISORS

The institution responsible for submitting the application, which is also responsible for coordinating the response for all the research unit's supervisory authorities, has not submitted any general comments

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