Research evaluation

EVALUATION REPORT OF THE UNIT

LBPC-PM - Laboratoire de biologie physico-chimique des protéines membranaires

UNDER THE SUPERVISION OF THE FOLLOWING ESTABLISHMENTS AND ORGANISMS:

Université Paris Cité - UP Cité

Centre national de la recherche scientifique - CNRS

EVALUATION CAMPAIGN 2023-2024

GROUP D

Rapport publié le 26/02/2024

High Council for evaluation of research and highter education

In the name of the expert committee :

Andréa Dessen, Chairwoman of the committee

For the Hcéres :

Stéphane Le Bouler, acting president

Pursuant to 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:	Ms Andréa Dessen, CNRS - Centre national de la recherche scientifique, Grenoble
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Ms Ina Attrée

REPRESENTATIVES OF SUPERVISING INSTITUTIONS AND BODIES

Mr Lortat-Jacob Hugues, CNRS
Ms Boutin Emilie, UPC
Mr Coll Patrice, UPC

CHARACTERISATION OF THE UNIT

- Name: Laboratoire de biologie physico-chimique des protéines membranaires
- Acronym: LBPC-PM
- Label and number: UMR 7099
- Composition of the executive team: Mr Bruno Miroux (DU), Mr Martin Picard (acting DU from 01-01-2024 to 31-12-2024 and proposed DU for the next contract)

SCIENTIFIC PANELS OF THE UNIT

SVE Sciences du vivant et environnement
SVE3 Molécules du vivant, biologie intégrative (des gènes et génomes aux systèmes), biologie cellulaire et du développement pour la science animale

THEMES OF THE UNIT

The unit is organised as a single team, with researchers working in subtopics/themes of their choice. These themes do not represent subgroups, since the unit wishes to be considered and evaluated as a whole

The major themes of the unit include:
1. Energy coupling and supramolecular assembly of electron transfer chain
2. Molecular signalling of G protein-coupled receptor (GPCR)
3. Transport and membrane dynamic in bacteria
4. Molecular synthesis of Amphipols and ligands & Biophysical Approaches

HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

The LBPC-PM is located within the Institute of Physical and Chemical Biology (IBPC), which lies within the campus of Paris Sciences Lettres University. This campus also includes the ENS, the Curie Institute, Chimie-ParisTech and other notable schools. In addition, the unit is in close proximity to the Collège de France and UFR de Pharmacie (Faculté des Sciences, Université Paris Cité). Importantly, the unit is closely associated with the Department of Biology of Paris-Cité University.

RESEARCH ENVIRONMENT OF THE UNIT

Collaborations between the unit and neighbouring institutes are very active. Projects developed in partnership include those dedicated to the study of the cytochrome *b6f* complex, leukotriene G-coupled receptors and Hedgehog proteins, and microbial gene expression, amongst other interests. Notably, labex, Equipex, and multiple ANR funding schemes promote the integrative and collaborative aspect of the unit.

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

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	1
Directeurs de recherche et assimilés	6
Chargés de recherche et assimilés	3
Personnels d'appui à la recherche	7
Sous-total personnels permanents en activité	**17**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	1
Post-doctorants	5
Doctorants	6
Sous-total personnels non permanents en activité	**12**
Total personnels	**29**

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
CNRS	0	8	7
UNIVERSITÉ PARIS-CITÉ	1	0	0
AUTRES	0	1	0
Total personnels	**1**	**9**	**7**

GLOBAL ASSESSMENT

The LBPC-PM is a unit supported by the CNRS and Université Paris Cité (UPC), and is located within the Paris Science Lettres University campus. The central research interest of the unit involves the study of membrane proteins, including the development of novel stabilising amphiphilic polymers, using structural biology, biochemistry, chemical synthesis, and biophysical approaches.
The unit profits from the richness of diverse campuses, thus being able to establish a number of fruitful collaborations and train students with different backgrounds. The unit functions as a 'single team', sharing materials and equipment, with different senior scientists participating in the training of students and postdocs within diverse projects. These projects were presented to the Hcéres committee as being within four different themes that were often intertwined, a reflection of the unit's successful 'single team' functioning mode.

Strong points within the unit's trajectory include their mechanistic approach to studying signal transduction by GPCRs, efflux pumps, and heme import pathways (i.e. projects involved in Themes 2, 3 and 4), which have led to publications in very good to excellent journals (such as Biochemistry, Comm. Biol., J. Sruct. Biol., Nat. Comm.). The committee wishes to underline that despite the heterogeneity in the choice of journals, the scientific production can be considered ranging from very good to excellent (i.e., the characterisation of the ExbB/HasB interaction in *Serratia marcescens*, published in Comm Biol; the study of the dynamic interplay between lipids and membrane proteins by hydrostatic pressure, published in Nat Commun, and a review article on applications of inducible intracellular membrane systems, published in Microb. Cell Factories).

In addition, the unit was supported by a number of grants within the evaluation period (9 total ANR projects, of which two were coordinated by members of the unit; one Equipex project, one Marie Sklodowska-Curie Action grant, and one labex project, the latter is coordinated by the unit), underlining its capacity to successfully attract funding for its different projects. Notably, despite difficulties with building comfort (such as the fact that the unit is located within different floors of the building), the unit is seen as being attractive for PHD students (14) and postdocs (8), who assessed their working conditions very positively. The unit has also organised a number of meetings, including GDRs, Inserm workshops and the annual scientific day of the 'ABC of membrane transport' meeting. Members have been invited to give talks at conferences, including one invitation for a Gordon plenary conference during the evaluation period.

The unit has, in the past years, gained considerable international visibility thanks to the development of amphipols, molecules that have notable applicability in the stabilisation of membrane proteins. During the evaluation period, and despite the difficulties faced by the unit in terms of space and personnel, it was able to develop CycIAPols, novel amphipols with improved characteristics, which led to one exploitable patent and their worldwide commercialisation since 2022 by a company Cube Biotech. These recently developed molecules have been shown to diminish background issues in cryo-EM images of purified membrane proteins, an attractive development in a field of key international relevance; this work was recently published in Commun. Biol. In addition, the unit has also developed novel *E. coli* strains adapted for the improved expression of membrane proteins. This underlines the unit's tradition of excellence in what relates to projects involving value enhancement and innovation in the fields of membrane protein biochemistry and structural biology and is at the heart of their international reputation in the field of membrane proteins.

DETAILED EVALUATION OF THE UNIT

A – CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

Most of the weaknesses pointed out by the previous Hcéres panel were related to a potential weakening of the unit through (1) departures of experienced scientists and (2) the lack of space that does not allow the unit to expand. Two positions were lost: that of a solid-state NMR specialist who went on sabbatical and upon his return, chose to go to another laboratory, and a chemist research engineer. This loss was particularly critical and a replacement was provided by the CNRS but only at the level of 'ingénieur d'étude', which was not optimal as a replacement of a chemist within the environment of a biochemistry unit. The unit has also stated that the chemistry laboratory is not of the appropriate size and is not well equipped. Despite these difficulties, given that the unit is very well known for their chemistry work, notably on amphipols and other polymers, this is quite problematic.

The unit was able to recruit a second MCF in 2023 but to date the number of personnel associated with the university remains small (going hand-in-hand with the level of recurrent funding). The unit also sees this situation as a potential threat.

Regarding recommendations on the themes themselves, they were mostly concentrated on issues regarding specific scientists that were planning to retire and the interactions with the crystallisation and EM platforms. This seems to have been partly remediated, since two senior scientists will be remaining as emeritus, and the unit has obtained grants that can cover different topics. The Cacsice EM platform at the Pasteur Institute is being accessed by the unit and individual scientists are being trained on single particle data collection and processing as well as the use of a Vitrobot plunger and the Glacios microscope itself.

THEME 1

Previous recommendation: 'More interactions could be developed with the "Biochimie théorique" unit. In addition, the visibility could be further increased by organising international conferences. The proposed research plan is excellent and ambitious, but one PI could retire before the end of the next contract. In consequence, it is essential that more team members/leader be recruited.'

In order to address this question, the PI in question remained as an emeritus and is working with another senior scientist. A collaboration with the Laboratoire de Biochimie Théorique was initiated on the modelling of UCP1. However, the international visibility of the Theme still remains limited.

THEME 2

Previous recommendation: 'The Hedgehog thematic, in particular, is below the critical size for such a competitive project and would need additional support.' The Unit took this recommendation into consideration, since support in terms of funding via Labex Dynamo was awarded to this project. In addition, an ANR grant was obtained in 2022.

THEME 3

Previous recommendation: 'One PI (and his coworker) should be retired before the end of the next contract. Recruitment of a new PI could allow the continuation of a promising project. In addition, structural studies are performed outside the unit.
Interactions with the IBPC crystallisation platform and the Cacsice EM platform should be developed and strengthen. Development of new challenging projects (T3SS is one of the most extensively investigated secretion system) is attractive but highly competitive.'

The scientist who was considering retirement is now remaining as an emeritus scientist, and will continue a collaboration through an ANR obtained with the Pasteur Institute (HasA/HasR project). The heme transport project has also been supported by the arrival of a new scientist as well as involvement in the Cacsice EM platform. The recommendations of the previous panel have thus been taken into consideration.

THEME 4

Previous recommendation: 'A major threat is the potential departure of the technical support in charge of organic chemistry synthesis of amphipols and of various ligands, useful for the structural investigation of *b6f* and UCPs'

The recruited chemist engineer IE-CNRS wishes to leave the lab due to lack of space and adapted equipment. The most immediate solution acted upon by the unit thus includes the limitation of the complexity of chemistry synthesis goals and the expansion of collaborations for more challenging chemical synthesis projects.

B – EVALUATION AREAS

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

The unit displays five notable scientific objectives, including (1) establishment of in-house cryo-EM related methodologies, (2) establishment of technologies to understand the role of lipids in membrane protein functions, (3) development of quantitative assays for the analysis of membrane transport systems, (4) integration of in silico approaches into experimental models, and (5) the generation of new polymer surfactants. These objectives have been either fulfilled fully or to an appropriate extent, despite the challenges encountered, using the resources at the unit's disposal.

Assessment on the unit's resources

The unit's scientific recognition as well as the onsite and offsite collaborations with other UMR/UFR organisations within Paris have solidified the unit's capacity to obtain or renew selective grants (ANR, MSCA-Cofund labex, MITI, Equipex), partly with scientists from the unit as project coordinators. The CNRS and University also provide a contribution to the unit's total resources. One difficulty seems to be that the laboratories that compose the unit are located within three different floors, and reorganisation attempts have failed.

Assessment on the functioning of the unit

The unit works mostly quite well, as a 'single team', and has a clear mindset in what relates to human resource fairness and equal treatment. Unit members are concerned about gender equality as well as the well-being of a handicapped member. Data management and protection are guaranteed through the use of common & well-established scientific resources, as well as the deposition of structural biology data in international databases. Some weak points include problems with the chemistry lab that led to a workplace accident and the absence of a centralised unit for data storage (notably EM images).

1/ The unit has set itself relevant scientific objectives.

Strengths and possibilities linked to the context

General comments:

The themes during the 2017–2022 evaluation phase were:

1. Energy coupling and supramolecular assembly of electron transfer chain
2. Molecular signalling of G protein-coupled receptor (GPCR)
3. Transport and membrane dynamic in bacteria
4. Toolbox for membrane protein study

The strengths of the unit lie in its unified/overlapping themes, with scientists providing support to others in the unit within their specialties. The scientific strength and international recognition of the unit are very clear in the areas of transport and membrane dynamics in bacteria and molecular synthesis of amphipols and other probes. The unit has numerous successful collaborations, as seen by the high number of ANR grants (especially considering the small number of scientists in the unit).

THEME 1

Theme 1 involves two main projects, notably the study of respiratory chain complexes and the mitochondrial uncoupling protein. During the period, the unit contributed towards an understanding of the signalling process of cytochrome *b6f* in the green alga *C. reinhardtii* as well as the development of homology models of UCP1 followed by molecular dynamics simulations and biochemical tests to understand the action of activators and inhibitors. In terms of publications, Theme 1 highlighted Plant Physiol (2018) and PNAS (2017) with a unit member as the second author, as well as two review articles (Chem Rev 2018 and Methods 2018) with a unit member as co-author. UCP1-related publications with a unit member as the last author involved an article in Febs J in 2021 and one paper in press in Nat Comm, that was published in 2023.

Theme (1) is being financed by ANR and a PHD fellowship. The ANR is coordinated by a collaborator from outside the unit.

THEME 2

Theme 2 focuses on one of the main families of membrane receptors, the GPCR family. Conformational plasticity of GPCRs is a key characteristic of their mechanism of signal transduction. The conformational landscape of GPCRs remains to be described in an appropriate lipid context as the latter can significantly impact the dynamics and conformations of membrane proteins.
This theme is divided into two projects: the study of the Hedgehog (Hh) signalling pathway and the study of the influence of lipids on GPCR conformation and dynamics.

Project1. The deregulation of the evolutionarily conserved Hedgehog (Hh) pathway is associated with pathologies such as cancer. Using circular dichroism, SAXS and molecular modelling in collaboration with the UPR9080 in IBPC, insect and vertebrates SuFu (Suppressor of Fused) were shown to display distinct structures (J Struct Biol. 2022). In collaboration with IPMC Sophia Antipolis and the University of Nice, molecular interactions between an inhibitor and Hh Patched were characterised and will be further analysed by cryo-EM. The 'Patched-Sensor' ANR grant, coordinated by the Curie Institute, was obtained with unit members as partners to study Hh Patched auto-association.

Project 2. In collaboration with IBMM (Montpellier) and the ICSN, the laboratory showed how lipids influence allosteric modulation of ghrelin receptor signalling (Nature Communications, 2021). Also, they used the association of high-pressure NMR on GPCRs incorporated into nanodiscs to address, at the atomic scale, the close dynamic relationships between lipids and this receptor (Nature Communications, 2022). The laboratory has acquired a recognised expertise, at the national and international levels, on the impact of lipids on the dynamics and conformations of membrane proteins such as GPCRs.

Theme 2 is supported by three ANR grants. Fellowships have been obtained for PHD students and postdocs.

THEME 3

Research within this theme aims at understanding molecular machinery involved in the export & import of molecules through the bacterial membrane. The groups involved employ structural biology, biochemistry, and biophysical strategies to understand efflux pumps and heme/iron acquisition systems that depend on TonB-dependent transporters. Of particular interest is the effort made by the groups in developing methodologies not only to understand the structural biology and biochemistry of membrane protein complexes, but also to measure transport in quantitative, real-time fashion.

The unit has been at the forefront of ways to improve membrane protein overexpression and purification for many years developing unique E. coli strains that often overcome the pitfalls of protein expression. Building on the foundations of a previous study, a thorough data mining performed in collaboration with Leeds Univ. led to the rationalisation of the conditions for overexpression, in *either E. coli* or yeast, and purification of membrane proteins of known 3D structures (Methods, 2018). In line with this, they developed new *E. coli* strains (i.e. C44 – DE3 – and C45 – DE3) with improved yield and quality for membrane protein overproduction (Sci Rep, 2018) and they modified the well-known C41 (DE3) and C43 (DE3) strain, in coll. with a lab in Dusseldorf (Germany), to create strains deleted in the acrAB and ompF genes (Microb. Cell Factories, 2019).

Theme (3) is supported by four ANR grants, one of which is coordinated by a scientist from the unit.

THEME 4

The unit is also very well known for the development of compounds that stabilise membrane proteins after solubilisation by classical detergents, such as amphipols. These include innovative cycloalkane-modified amphiphilic polymers, called CyclAPol. In contrast to classical amphipols, these new molecules are capable to efficiently extract membrane proteins and show a better stabilising effect than SMA co-polymers (Biomacromolecules, 2020; Anal. Chem., 2022). These new polymers maintain the native lipids associated with the membrane protein and this is currently addressed by mass spectrometry for the nicotinic acetylcholine receptor in the frame of an ANR project (Prolific) and in coll. with the Pasteur Institute. In collaboration with physicists (CNRS-Université Paris-Saclay), the role of two types of surfactants (i.e. DDM *vs* A8-35) during the vitrification step for Cryo-EM studies were investigated and the amphipol appears rather promising as compared to the detergent (Biophys. J. 2023).

Finally, by using a combination of biophysical techniques (i.e. Sec-Malls, Sec-Saxs and MD simulations), the complex between the heme/hemoglobin outer membrane receptor ShuA from *Shigella dysenteriae* and DDM was thoroughly characterised (BBA Biomembranes, 2021).

In theme (4), a possibility to open another platform through the Dynamo2 labex dedicated to insect cell production of membrane proteins is envisaged.

Weaknesses and risks linked to the context

Overall

The main threat concerns the limited capacity of the Chemistry lab to further develop CyclAPols in the future due to both the departure of the engineer in charge of the synthesis of the polymers and the undersized chemical hood for some large-scale syntheses. One of the main research subjects of the unit that has had the most international recognition has been related to amphipol synthesis and membrane biochemistry, and with the absence of appropriate facilities for the chemistry effort this very interesting and promising research could be compromised.

The lack of space limits the unit's attractiveness potential as well as the potential upgrade of the collaborative space for the platforms. New recruitment includes an assistant professor ('maître de conférences' from the University), supposedly to add more balance between the contributions of the CNRS and the University. However, it is of note that the new MCF is expected to have a high teaching load and thus will not be able to work full-time in the lab, and there is a considerable distance between the teaching building and the IBPC premises.

THEME 1

The theme is promising and interesting but merits the dedication of more full-time researchers and support from further ANR grants.

THEME 2

The scientific link between the two projects of theme 2 is rather tenuous.
In addition, the number of scientists associated with theme 2 is low (already mentioned in the previous Hcéres report). Both points have been already taken into consideration by the unit, as they propose a novel organisation for the next five years, where project 1 (Hedgehog – Hh – signalling pathway) is included in a 'Membrane protein transport' theme. As for project 2 (GPCR dynamics and lipid influence), it will be associated with other projects of the unit that deal with the impact of lipids on the conformational dynamics and activity of membrane proteins.

THEME 3

It is unclear where the boundaries are between Themes 3 and 4. Projects and objectives described as being part of Theme 3 in the 2017–2022 timeframe are presented as part of Theme 4 in the 'Prospective' section. This supports on one hand that there is overlap and collaboration within the unit, but also suggests that there should be a clearer distinction/discussion about the themes that include these projects.

THEME 4

The section dealing with 'Shaping bacterial cells for Eukaryotic membrane proteins production in E. coli' has been associated with theme 3 by the unit, but appears more related to theme 4. As a matter of fact, this part is

both associated with themes 3 (project 'Syborg' for Synthetic Bacterial Organelle) and 4 (Membrane protein production and solubilisation, a global analysis) in the unit trajectory. Likewise, the use of CyclAPols for GPCRs studies is included in theme 3 but the technological development of these molecules is in theme 4, both in the past achievements and trajectory.

2/ The unit has resources adapted to its activity profile and research environment, and makes use of them.

Strengths and possibilities linked to the context

General comments:

All of the themes are funded principally by the ANR, with unit scientists acting either as coordinators or collaborators; moreover, the Equipex and labex programs secure the maintenance and renewal of the instruments. The expertise of the unit is clearly recognised at the level of the two doctoral schools, which provide fellowships for students interested in performing research in the unit. The highly competitive MSCA-Cofund postdoctoral program is also beneficial to the international character and visibility within the EU research area.

In what relates to equipment, five FPLC instruments, common rooms for centrifugation, cell disruption, Typhoon, bacterial incubators, fluorimeter, stop-flow systems are shared. In addition, the unit has access to three platforms for structural biology studies: X-ray crystallography, NMR, and mass spectrometry.

THEME 1

It involves one CR, three IEs, one DR Inserm, one MCF, one DR CNRS, one AI, one IR, two DRs CNRS, as well as postdocs and interns. Most of the permanent personnel involved in the Theme are also heavily involved with other themes, which could explain why this theme has been less productive than others. Three PHD students defended their theses during the evaluation period and one thesis is ongoing.

THEME 2

This theme concerns three researchers (1CR, 1DR, 1 MCF), and all are involved in at least a second theme. In addition, one Technician (2 themes) and two research engineers (involved in 2 and 3 themes, respectively) participate in theme 2. In the period, one CDD contract and three postdocs have worked in Theme 2, as well as seven students for short internships.

One PHD student defended a thesis in 2017 while another student started a PHD in 2022.

THEME 3

It is supported by one CR, one DR CNRS, one IE, one DR Inserm, three DR CNRS, one MCF, one tech CNRS, as well as postdocs, trainees and students. Several of the permanent members also work in other themes, while most of the non-permanent members tend to work on a unique theme. Two PHD theses were defended during the evaluation period.

THEME 4

It is supported by one CR, four DR CNRS, one IR, two IEs, two IRs, one DR Inserm, one MCF, as well as postdocs and students. three PHD students defended their theses during the evaluation period, and one thesis is ongoing.

This axis has been supported by the labex Dynamo as well as by two consecutive ANR grants (Genecaps and Fliposome) and by another ANR (Prolific) so the different projects appear very well funded.

Weaknesses and risks linked to the context

The recurrent funding is clearly not enough to maintain the high-end instrumentation. In addition, the unit has a problem of space, especially in what relates to a chemistry laboratory, as mentioned above. Negotiations to address this issue, as well as to address the fact that the unit itself exists in three different floors of the building, were initiated but did not succeed. It is thus commendable that the unit is so successful despite these shortcomings that have not been addressed by the relevant administrations. The panel agrees that negotiations regarding the unit's space problem are critical and must be pursued so that a solution be reached allowing the natural growth of the unit in the years to come.

3/ The unit's practices comply with the rules and directives laid down by its supervisory bodies in terms of human resources management, safety, the environment, ethical protocols and the protection of data and scientific heritage.

Strengths and possibilities linked to the context

The weekly meetings, the training courses and the officers for safety, environment and IP are signs that the unit functions very well. There is a clear gender plan. In the past five years, the overall composition of the unit has reflected that, with at least 50% of researchers/students being female. There is cohesiveness not only in scientific interests but also between the scientists themselves.

An environmental transition plan is in place and several steps have been taken to reduce the unit's carbon dioxide footprint, including efforts developed in partnership with the city of Paris.

Weaknesses and risks linked to the context

Despite the clear effort that has been made in terms of gender equality, it is unclear how many women have access to leadership positions. Regarding security, as already mentioned in another section, the quality of the chemistry lab has already led to a workplace accident and the improvement of the quality of this laboratory should be looked into.

The unit is expanding its efforts in cryo-EM, which generates large amounts of data that must be stored securely, requiring the availability of additional storage space.

EVALUATION AREA 2: ATTRACTIVENESS

Assessment on the attractiveness of the unit

During the evaluation period, the unit was supported by numerous grants from different funding bodies. This underlines the unit's capacity to successfully attract funding for its different projects despite its small size. The panel would like to encourage the unit to expand their attractiveness by encouraging applications to ATIP and ERC funding schemes, although the lack of space is clearly an issue.

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

General comments:

The work developed by the unit in terms of membrane protein biochemistry and biophysics, especially the development of amphipol technologies and the development of bacterial expression hosts for membrane protein production, are clearly recognised at an international level. In the past five years the unit has organised a number of international and national meetings and symposia. Scientists that work within the unit also hold key roles in scientific societies and councils, as well as in labex and Equipex projects.

An additional attractive point of the unit includes the fact that a number of students and researchers have had access to hands-on training in electron microscopy, NMR, SEC-Mals, Mass spec, AUC, small angle scattering, and X-ray crystallisation. This is a central, important role of the unit and contributes significantly to its attractiveness. The high level of student co-supervision partnerships and collaborations is also a strong point of the unit. In addition, most of the publications of the unit in the past five years are 'open archive', either in HAL or BioRxiv.

Lastly, the unit has been very successful in attractive funding, including numerous ANR projects, labex, Equipex, and the EU Cofund program. ANR and MSCA-Cofund are a clear mark of the attractiveness at both undergraduate and post-graduate levels. The number of nationalities within the personnel is an index of international recognition, as well as the invited seminars at prestigious conferences, such as the Gordon conference series.

THEME 1

Scientists involved in Theme 1 have very good to excellent visibility. They have participated in and organized national conferences, participated in European symposia, and given 2 international conferences.

THEME 2

The theme has an excellent national and international visibility, as shown by the invitation in national and international conferences (15 conferences during the period). PIs of the theme were invited in three international meetings in the following conferences: 'International workshop on advanced isotopic labelling methods' in 2017, 'Gordon research conference on membrane protein folding' in 2017 and 'GPCR workshop', in Hawai, in 2019. In addition, a book chapter 'NMR Spectroscopy for the Characterisation of GPCR Energy Landscapes' in Structure and Function of GPCRs was published in 2017, demonstrating the attractiveness of the theme in the field of GPCR structures.

THEME 3

Scientists involved in Theme 3 have very good to excellent visibility, including the organisation of Inserm workshops, GDRs, annual scientific days, and symposia. They also hold key positions in national scientific organisations, such as the SFBBM and the AFC. There was a keynote lecture given at a Gordon conference and scientists within the theme have several collaborations within Europe.

THEME 4

The national and international visibility of this theme is excellent as the lab members involved have been pioneers in the field of overexpression of membrane proteins and the development of surfactants to preserve the structure and functionality of membrane proteins in solution. The efficient tools developed by them to optimise these two parameters are widely used and recognised worldwide by many scientists in the field of membrane proteins, and any improvement to purify and characterise these delicate proteins is warmly welcomed by the community. Scientists involved in the theme have several national and international collaborations with renowned scientists (e.g. Pasteur Institute, Germany).

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

General comments:

Most of the ANRs held by the unit involve the participation of the unit's scientists as collaborators; few scientists are ANR coordinators.

Platforms and equipment need to be maintained at international standards, and the lack of physical space for research is a threat for the unit. If more space is not obtained, this could have a clear negative impact on the unit. More specifically, Dynamo-2 and Cacsice, which end in 2024, allow the covering of costs of access to a 700Mhz solid/liquid NMR instrument, mass spectrometer, Titan and Glacios Cryo-EM facilities at the Pasteur institute. If these grants are not supported by other types of funding, access to these facilities, that are essential for the research of the unit, may be seriously hampered.

EVALUATION AREA 3: SCIENTIFIC PRODUCTION

Assessment on the scientific production of the unit

The scientific production of the unit is very good to excellent and reflects the unit's dedication to understanding membrane protein dynamics, structure, and biochemistry at the mechanistic level, as well as training young scientists and contributing to 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

General comment: All papers are in Hal or in Biorxiv or published in open access. The methodological papers are in specialist journals, while the scientific results are mostly in generic multidisciplinary medium-to-highly quality journals.

THEME 1

The scientific production of Theme 1 is very good. Theme 1 presented Plant Physiol (2018) and PNAS (2017) with a unit member as the second author, as well as two review articles (Chem Rev 2018 and Methods 2018) with a unit member as co-author. UCP1-related publications with a unit member as the last author involved an article in Febs J in 2021 and one paper in press in Nat Comm, that was published in 2023.

THEME 2

Theme 2 has generated nine papers among which six are articles with corresponding authors of the unit, including publications in Nature Commun. in 2022 (themes 2 & 4), Journal of Structural Biology (2022), Communications Biology (2021) (Themes 2 & 3), Molecular and Cellular Endocrinology (2019), Biochemistry (2018), and Scientific Reports (2017). Additionally, research performed with collaborators has been published in Nature Commun. (2022), Elife (2021) and Cancers (2020), demonstrating the high level of scientific production as well as the excellent collaborations.

THEME 3

The publication and funding levels of the scientists that work on this theme is very good to excellent and include Comm Biol (2021 and 2022), Sci Rep (2018) with unit members as last authors, and Nat Comm (2020), and Angew Chem (2019) with unit members as co-authors.

THEME 4

The scientific production is of very good to excellent (Methods, 2018; Sci Rep, 2018; Microb. Cell Factories, 2019 plus a review in the same Journal in 2020; Angewandte Chem. Int. Ed Engl. 2019; Biomacromolecules, 2020; Anal. Chem., 2022; Biophys. J. 2023; BBA Biomembranes, 2021; and a patent deposited on the CyclAPols and one chapter of a book in 2022) and is quite proportional to the number of people involved in this theme.

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

Themes 2, 3 and 4 have displayed a strong publication profile, with the methodology-related theme having notable recognition. Considering that these themes can be dependent on innovations in chemistry and it is specifically the chemistry laboratory that represents the major issue, this is a clear weakness that should be addressed.

90% of the publications of the unit are produced by three of the four Themes (2, 3 and 4), as the unit states in their self-assessment document. This indicates that the remaining Theme is involved in a minority of publications, and that there is heterogeneity within the unit itself in terms of scientific production and recognition.

In addition, more joint publications are needed to really strengthen the unit as a whole.

EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

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

As mentioned in other sections, the unit has clear recognition at an international level of its efforts in the chemistry of amphipols and membrane protein biochemistry and biophysics. Their activities related to student/postdoc training are also very strong and contribute to their clear attractiveness.

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 is totally dedicated to the scientific community at large, as their results have helped researchers involved in membrane protein biology and complex characterisation. Their synthesis products are commercialised and hopefully will provide further funds for their budget (CyclAPols have been patented and commercialized by Cube Biotech – since 2022).

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

The unit is only modestly involved in science fairs and in open access days. Their knowledge and expertise should be shared with the wider public/society to increase awareness of the importance of a molecular understanding of specific processes as a basis to the development of applications.

ANALYSIS OF THE UNIT'S TRAJECTORY

The recommendations from the past evaluation were fulfilled to the best of the ability of the unit, and the project for the next five years includes a reassessment of the four themes. The research and HR plans will reinforce and improve the trajectory of the unit in the next future.

Continuation of the chemistry effort within the unit can be achieved for straightforward and well-established synthesis goals. If more sophisticated chemistry efforts are envisioned, this can potentially be developed in collaboration with external groups, since at the moment the chemistry premises do not allow for complex syntheses and/or projects.

The committee also wishes to highlight the importance of recruiting new young scientists to the unit, given the high number of senior/emeritus scientists within the small organisation. This could be through ATIP or ERC young investigator grants, and could be facilitated by building renovations that have already been initiated (that could allow for the reorganisation of lab spaces) or that are foreseen for the near future. Regarding ANR grants, increasing the number of grants directly coordinated by scientists from the unit could further expand the unit's visibility.

RECOMMENDATIONS TO THE UNIT

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

Theme 2. 'Dynamics of membrane transport' and Theme 3. 'Conformational dynamics and stabilisation of membrane proteins in their lipid membranes' might be grouped in a single theme: 'Dynamics of membrane proteins'.

Theme 4. 'Toolbox for membrane protein studies'. The 'Syborg' project might be included in this theme, as it nicely fits within this axis and it will allow to re-equilibrate the different themes (theme 4 appears rather small as it stands).

Recommendations regarding the Evaluation Area 2: Attractiveness

As mentioned in other sections, the panel wishes to recommend that the unit hire new scientists, notably through ATIP and/or ERC calls, which will be important not only for unit livelihood but also for continuation of the funding schemes, although the committee acknowledges that space limitation is clearly an issue here.

Recommendations regarding Evaluation Area 3: Scientific Production

In some of the themes, the majority of publications have scientists from outside the unit as senior authors. This also seems to be the case for ANRs, that seem to be mostly coordinated by scientists from outside the unit. This issue should be addressed in order to expand the unit's international visibility.

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

The panel agreed that one clear strong point of the unit was the contribution of its research activities to scientific community and society, and wishes to encourage it to pursue in this path.

CONDUCT OF THE INTERVIEWS

Date

Start: 05 décembre 2023 à 8 h 30

End: 05 décembre 2023 à 17 h 30

Interview conducted : online

INTERVIEW SCHEDULE

December, 5th, 2023

Laboratory of Physical and Chemical Biology of Membrane Proteins

LBPC-PM - UMR7099

DU : Bruno Miroux
Deputy Director / Next contract: Martin Picard

Committee
Chairwoman: Andréa Dessen ; Experts : Jean-Michel Jault (Expert Panel SVE3), Isabelle Krimm (expert CoNRS), Adriana Erica Miele (expert CNU), Michel Thépaut (expert PAR)
Hcéres scientific advisor (CS): Ina Attrée

8:30 Test Zoom connections (CS-DU)
8:40 – 8:50 Closed session_Committee + CS only

Scientific sessions

8:50 – 9:00 Introduction / Presentation of the Committee members

9:00 – 9:45 Unit presentation by the DU (30'+ 15' discussion) B. Miroux

Break – debriefing committee (15')

10:00 –10:40 2 Talks (2x20 min, 10' talk + 10' discussion)

10:00-10:20	**Theme 1** *Energy coupling and supramolecular assembly of electron transfer chain* (F. Zito)
10:20-10:40	**Theme 2** *Molecular signalling of G protein-coupled receptors* (L. Catoire)

Break/debriefing committee (15')

10:55- 12:15 4 Talks (2x40 min, 2x10' talk + 20' discussion)

10:55-11:35	**Theme 3** *Transport and membrane dynamics in bacteria* (V. Biou, M. Picard)
11:35-12:15	**Theme 4** *Toolbox for membrane protein study* (M. Zoonens, K. Moncoq)

Lunch/debriefing committee (60')

13:15 –13:45 Meeting w/ **Supervising bodies** (CNRS, UPC)

Interviews
13:45- 14:15 Meeting w/ technical staff
14:15 LBPC_private meeting
Meeting ID: 930 3478 6957 / Passcode: 670152

14:30– 15:00 Meeting w/students

15:15– 15:45 Meeting w/researchers and EC (no DU)

Break – debriefing committee (15')

16:00- Discussion between Committee and DU (M. Picard, B. Miroux)

Closed session_Committee discussion/Report

Campagne d'évaluation 2023-2024– Vague D

GENERAL OBSERVATIONS OF THE SUPERVISORS

Université Paris Cité

Le Président

Paris, le 31 janvier 2024

HCERES
2 rue Albert Einstein
75013 Paris

Objet : Rapport d'évaluation de l'unité **DER-PUR250024234 - LBPC-PM - Laboratoire de biologie physico-chimique des protéines membranaires**

Madame, Monsieur

L'Université Paris Cité (UPCité) a pris connaissance du rapport d'évaluation de l'Unité de Recherche **LBPC-PM : Laboratoire de biologie physico-chimique des protéines membranaires**

Ce rapport a été lu avec attention par la direction de l'unité, la vice-doyenne recherche et le doyen de la Faculté des Sciences d'UPCité dont vous trouverez ci-joint un courrier incluant en annexes les remontées de l'unité (cf courrier joint), par la vice-présidente recherche d'UPCité et par moi-même.

Je n'ai pas d'observations d'ordre général à apporter.

Je vous prie d'agréer, Madame, Monsieur, l'expression de ma considération distinguée.

Édouard Kaminski

Présidence

Référence
Pr/DGDRIVE/2023

Affaire suivie par
Christine Debydeal - DGDRIVE

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85 boulevard St-Germain
75006 - Paris

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Laboratoire Biochimie des Protéines Membranaires (BPM UMR 7099)

Institut de Biologie Physico-Chimique (IBPC)

Martin PICARD, Ph.D, HDR.
Directeur d'unité, Laboratoire Biochimie des Protéines Membranaires (BPM),
CNRS UMR 7099 / Université Paris Diderot
13, rue Pierre et Marie Curie
75005 Paris

Objet : Observations de l'unité relatives au rapport d'évaluation des experts Hcéres
ref. D2025-EV-0755976N-DER-ER-DER-PUR250024234-SVE3-LBPC-PM-RT

Paris, le lundi 22 janvier 2024

Madame, Monsieur,

Je fais suite au mail du 12/01/2024 dans lequel vous nous communiquiez le rapport d'évaluation Hcéres de l'UMR7099. Je vous fais part ci-dessous des observations de portée générale relevées et discutées au sein du laboratoire à l'occasion d'une réunion dédiée.

Tout d'abord, les membres de l'unité tiennent à remercier les différents experts pour le temps qu'ils ont consacré à l'examen de l'unité et des différents thèmes qui la composent.

Nous sommes très satisfaits de lire que le comité a reconnu la qualité de notre recherche, notre visibilité nationale et internationale en tant que laboratoire de référence dans l'étude des protéines membranaires et qu'il a mis en avant l'originalité et la force de notre mode de fonctionnement mono-équipe et les bénéfices qu'en tirent chacun des membres du laboratoire d'un point de vue scientifique et humain ("strength of the unit: unified/overlapping themes, with scientists providing support to others in the unit within their specialties", p. 8).

Comme de juste, le comité pointe les enjeux et risques relatifs à la ré-orientation de notre stratégie scientifique concernant la chimie de synthèse organique. Les diagnostiques et recommandations du comité sont pleins de bon sens mais deux paragraphes nous apparaissent toutefois en contradiction. D'une part, le paragraphe "Weaknesses and risks linked to the context" (Evaluation area 1, assessment on the scientific objectives of the unit) dit que les capacités limitées du laboratoire de chimie pour continuer à développer les CyclAPols met en péril les perspectives de recherche concernant cette série de molécules très prometteuses et, plus largement, la reconnaissance internationale acquise par le laboratoire concernant la synthèse des amphipols et la biochimie membranaire (cf. page 9: "[…] main threat concerns the limited capacity of the Chemistry lab to further develop CyclAPols in the future […] One of the main research subjects of the unit that has had the most international recognition has been related to amphipol synthesis and membrane biochemistry, and with the absence of appropriate facilities for the chemistry effort this very interesting and promising research could be compromised.)

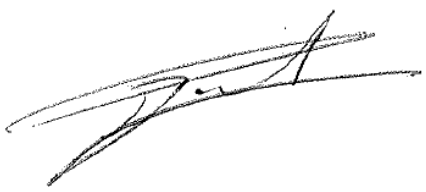
Comme mentionné dans notre document d'auto-évaluation, nous assumons la décision de ne pas engager plus avant d'efforts dans le développement de nouvelles générations de molécules en interne pour l'instant mais: i) nous sommes ouverts à travailler dans cette direction en collaboration avec d'autres laboratoires de chimie (nous avons d'ailleurs engagé des démarches récentes en ce sens), ii) les développements des CyclAPols occuperont une place centrale pour le prochain mandat puisque nous envisageons de caractériser les bénéfices de fonctionnalisations chimiques pour cette nouvelle famille de molécules. Les enjeux et les potentialités sont d'autant plus grands que nous avons à disposition une grande variété de CyclAPols qui sont des polymères amphipathiques différant par le type de cycloalcane utilisé (cyclohexylethylamine ou cyclooctylamine) mais aussi par la densité des groupes hydrophobes, le nombre d'atomes de carbone et la densité de charge des polymères. Dans ce contexte, la combinatoire de molécules potentiellement étudiées est très grande et nous comptons bien continuer à porter haut ce domaine de recherche pour lequel nous avons effectivement une réputation internationale à tenir !

De ce point de vue-là, la recommandation finale sur la trajectoire du laboratoire nous apparaît beaucoup plus en ligne avec notre vision de l'avenir de ce champ de recherche :
"Analysis of the Unit's trajectory (page 15): Continuation of the chemistry effort within the unit can be achieved for straightforward and well-established synthesis goals. If more sophisticated chemistry efforts are envisioned, this can potentially be developed in collaboration with external groups, since at the moment the chemistry premises do not allow for complex syntheses and/or projects".

Nous souhaiterions également commenter la recommandation du comité relative à la fusion des thèmes 2 ("dynamique du transport membranaire") et 3 ("Dynamique conformationnelle et stabilisation des protéines dans leurs membranes lipidiques"). Cette proposition est séduisante sur le papier mais nous pensons qu'elle aurait pour conséquence de déséquilibrer dramatiquement les thèmes alors que notre nouvelle proposition de répartition des thèmes avait justement pour vocation de donner des axes plus cohérents dans leurs objectifs scientifiques et plus équilibrés pour ce qui concerne le nombre de personnes impliquées.

En vous remerciant d'avance de l'attention que vous porterez à ces ultimes commentaires, je vous prie de croire, Madame, Monsieur, l'expression de mes respectueuses salutations.

Martin Picard



Marine MADANI

De: CNRS-Hcéres Evaluation unités
Envoyé: mardi 23 janvier 2024 16:34
À: Hcéres-Ged
Objet: RE: Hcéres - demande de retour des observations des tutelles sur le rapport d'évaluation - DER-PUR250024234 - LBPC-PM - Laboratoire de biologie physico-chimique des protéines membranaires

Madame, Monsieur,
Je vous remercie de nous avoir transmis de ce pré-rapport et prie de bien vouloir noter que le CNRS n'émettra pas de réponse institutionnelle de type « observations de portée générale ».
Je reste à votre disposition pour tout complément d'information.
Bien à vous,

--
Frédéric FRANCOIS-ENDELMONT
CNRS – DAPP
Direction d'appui aux partenariats publics

The Hcéres' evaluation reports are available online:
www.hceres.fr

Evaluation of Universities and Schools
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