Chimie biologique des membranes et du ciblage thérapeutique

Rapport Hcéres

agence d'évaluation de la recherche
et de l'enseignement supérieur

Department for the evaluation of research units

AERES report on unit:

Chimie Biologique des Membranes et Ciblage Thérapeutique

CBMCT

Under the supervision of the following institutions and research bodies:

Institut Curie

Centre National de la Recherche Scientifique

Institut national de la santé et de la recherche médicale

November 2012

agence d'évaluation de la recherche
et de l'enseignement supérieur

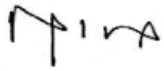
Research Units Department

President of AERES

Didier Houssin

Research Units Department

Department Head



Pierre Glaudes

The president of AERES "signs[...], the evaluation reports, [...]countersigned for each evaluation department by the relevant head of department (Article 9, paragraph 3, of french decree n°2006-1334 dated 3 november 2006, revised).

Grading

Once the visits for the 2012-2013 evaluation campaign had been completed, the chairpersons of the expert committees, who met per disciplinary group, proceeded to attribute a score to the research units in their group (and, when necessary, for these units' in-house teams).

This score (A+, A, B, C) concerned each of the six criteria defined by the AERES.

NN (not-scored) attached to a criteria indicate that this one was not applicable to the particular case of this research unit or this team.

Criterion 1 - C1: Scientific outputs and quality;
Criterion 2 - C2: Academic reputation and appeal;
Criterion 3 - C3: Interactions with the social, economic and cultural environment;
Criterion 4 - C4: Organisation and life of the institution (or of the team);
Criterion 5 - C5: Involvement in training through research;
Criterion 6 - C6: Strategy and five-year plan.

With respect to this score, the research unit concerned by this report and its in-house teams the following grades:

- Grading table of the unit: Chimie Biologique des Membranes et Ciblage Thérapeutique

C1	C2	C3	C4	C5	C6
A+	A+	A+	NN	A+	A+

- Grading table of the team: Endocytose et délivrance thérapeutique

C1	C2	C3	C4	C5	C6
A+	A+	A+	A+	A+	A+

- Grading table of the team: Dynamique et Mécanique Membranaires de la Signalisation Intracellulaire

C1	C2	C3	C4	C5	C6
A+	A	A	NN	A+	A+

- Grading table of the team: Chimie des biomolécules, des sondes, et des inhibiteurs hétérocycliques

C1	C2	C3	C4	C5	C6
A	B	A	A	A	A

Evaluation report

Unit name:	Chimie Biologique des Membranes et Ciblage Thérapeutique
Unit acronym:	CBMCT
Label requested:	UMR
Present no.:	
Name of Director (2012-2013):	M. Ludger JOHANNES
Name of Project Leader (2014-2018):	M. Ludger JOHANNES

Expert committee members

Chair:	Mr Bruno ANTONNY, Université de Nice-Sophia Antipolis
Experts:	Mr Gilles DIVITA, Université de Montpellier
	Mr Jost ENNINGA, Institut Pasteur, Paris (CSS INSERM representative)
	Mr Jean GRUENBERG, Université de Genève, Switzerland
	Mr Alain WAGNER, Université de Strasbourg (CNRS representative)

Scientific delegate representing the AERES:

Mr Pierre VIERLING

Representative(s) of the unit's supervising institutions and bodies:

Ms Chantal LASSERRE, INSERM

Mr Daniel LOUVARD, Institut Curie

Mr Jacques MADDALUNO, INC, CNRS

1 • Introduction

History and geographical location of the unit

This project involves two teams in biology and one team in chemistry from two distinct units of the Institut Curie, Paris. The staff of this new unit (7 permanent researchers and 5 permanent staff without research duties) is from Institut Curie, INSERM or CoNRS. The biologists, around Mr LUDGER JOHANNES and Mr Christophe LAMAZE, are part of the UMR 144 (director Mr Bruno GOUD), a leading laboratory in cell biology at the Institut Curie. They have been studying various aspect of cell endocytosis with a specific interest in new mechanisms of membrane deformation, cargo uptake and membrane mechanics. The chemists are from the UMR 176 (current director Mr Jean-Claude FLORENT), a unit with a strong expertise and history in organic chemistry for the synthesis of new bioactive molecules. By anticipating changes in the former UMR 176 with the retirement and move of several principal investigators, they propose to team up around Mr Frédéric SCHMIDT to form a group complementary to the aforementioned biologists. Overall and with the expected recruitment of a new principal investigator in chemistry, the unit should include four principal investigators and ambitions to become an important center in chemical biology. The biologists and chemists have already collaborated, especially during the last years. They will remain in their separated buildings (Bâtiment Burg / bâtiment Rossignol, respectively), which are within walking distance. Some adjustments have been scheduled to improve space use.

The main aim of the project is to foster new research and applications based on recent progress in membrane biology, notably the identification of new portals of entry into the cells by Teams 1 and 2. Improving the cellular uptake of therapeutic molecules depends on a better understanding of biological membranes. Conversely, the various mechanisms by which cells capture molecules or pathogens are inspiring for the discovery of novel drug delivery routes and probe design. Overall the project fits with the tradition of the Institut Curie to conduct basic, translational and clinical research thanks to the combination of researchers from different fields.

Management team

Mr Ludger JOHANNES, INSERM, will head the new research unit. The operational committee will include Team 2 and Team 3 leaders.

AERES nomenclature

SVE1_LS3 (principal); ST4 (secondary)

Unit workforce:

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions			
N2: Permanent researchers from Institutions and similar positions	8	7	7
N3: Other permanent staff (without research duties)	7 [5,8]	5	
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)			
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	9	9	1
N6: Other contractual staff (without research duties)	2	4	
TOTAL N1 to N6	**26** [24,8]	**25**	**8**

Percentage of producers	***100 %***

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	9	
Theses defended	12	
Postdoctoral students having spent at least 12 months in the unit*	17	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	8	7

2 • Assessment of the unit

Strengths and opportunities

Within the Institut Curie, two teams in biology have unraveled new mechanisms for cell entry using bacteria toxins and viruses and clarified the roles of small membranes structures named caveolae at the plasma membrane. Beside their importance in basic research, these remarkable pieces of work suggest interesting and innovative strategies for drug delivery and are inspiring for new approaches in which chemistry helps to understand biological processes (hence the name 'chemical biology'). Of note, this work has already been at the root of collaborations between chemists and biologists and of two startup companies. Chemists at the Institut Curie have had a strong interest in translational research for years, hence the idea of setting up of a single "unité de recherche" entitled "Chimie Biologique des Membranes et Ciblage Thérapeutique" in which chemists and biologists work in synergy.

The excellence of the research, the overall adhesion of the people to the project, the fair self-evaluation (the committee appreciated the SWOT analysis), and the support by the Institut Curie, INSERM and CNRS give firm grounds to the project.

Weaknesses and threats

Balance. Because of the strong history of the chemists as an independent research unit, the main risk is an unbalanced association in which chemistry is 'used' by biology but not the other way around. The main investigators are aware of this risk. Moreover, the committee thinks that the biological processes studied by Teams 1 and 2 should be inspiring for chemists and help them to create new molecules that may have broader interest, extending beyond their application. Indeed, one can notice that the biological structures studied by Team 1 and Team 2 urgently need better chemical description: caveolae and toxin-induced invaginations are intriguing from a chemical point of view because of their bilayer asymmetry, curvature, and unique protein structures (e.g. pentamers, hairpins). Probes adapted to these unique anisotropic environments will be welcome by the community. Since the risk that one field develops at the expense of the other is well understood by the main investigators, this risk is likely to be transcended by the new concepts and ideas that will be born from the association.

Location. Chemists and biologists will remain separated (but within walking distance). However, previous collaborative work between researchers of different fields has been very successful at the Institut Curie. Therefore and despite this physical separation, the environment seems well adapted for the creation of a chemical biology unit.

Interdependence. On a day-to-day basis, collaborative work at the interface between two fields is not easy to organize because progress is not necessarily in phase: for example, the time required for the design and synthesis of a new molecule does not necessarily match the bench work and/or interest of the biologist and vice versa. This interdependence has to be minimized especially during thesis works. Therefore, PIs have to check that, apart from the interfacial aspect of each project, there should be enough scientific work that can be conducted in an independent manner.

Competition. The committee noticed a potential overlap between one research line (cross-presentation) and works carried out by other teams in the Institut Curie. This point was recognized by the researchers and could also represent an opportunity for the sharing of expertise.

Recommendations

General. Biologists and chemists should continue their efforts to work together as this has already led to unique discoveries and applications.

The role of chemistry. From the mechanisms and structures studied by the biologists, chemists should identify issues that are associated with innovative synthesis or chemical strategies, not necessarily linked to immediate relevance in biology. In turn, biologists should make some routine systems or preparations available to chemists to help the development of innovative molecules. Put differently, the committee understands that part of the chemistry needed for vectorization (such as protein-drug coupling) is not necessarily innovative and cannot stimulate *per se* experts in chemistry. However, the committee considers that the mechanisms studied by the biologists are original (e.g. glycolipid clustering, membrane bending, membrane tension) and should inspire chemists. Biological membranes suffer from naïve and dubious descriptions because of the lack of expertise in chemistry of most biologists. The association between chemists and biologists is therefore very relevant in the field of biological membranes.

Training courses and continuing education. The majority of PhD students, post-docs as well as the main investigators from the two fields are positive about their future association. Special care should be taken, notably through training courses (e.g. those organized by the CNRS and INSERM) and shared lab meetings to make all technicians and engineers part of this challenging project. Considering that institutions generally encourage continuing education, the creation of a chemical biology unit should provide new opportunities for the technicians to develop their careers.

Interdependence. For works at the interface between chemistry and biology, the unit/teams should minimize time mismatch and try to keep some works that can be valued through specialized publications, besides major publications of general impact.

3 • Detailed assessments

Assessment of scientific quality and outputs

The research conducted by Team 1 and 2 leaders is extremely innovative. Their landmark works were published in the most prestigious journals (Shiga-induced endocytosis in *Nature*, membrane fission in *Cell*, caveolae as membrane tension sensors in *Cell*) and resulted in world-wide attention and recognition, as witnessed for example by (1) invitations in the best international conferences (e.g. ASCB, EMBO, Gordon), (2) invitations to write reviews in the best journals (1 x *Trends in Cell Biology*, 2 x *Cell*), (3) an election as an EMBO member (L Johannes). There are not many teams in the world with such a high level in membrane biology. Despite a less international exposure, the chemists around Team 3 leader are well recognized at the national level. Moreover, and this aspect is noticeable in the context of the unit creation, they have been collaborating in a very fruitful manner with the biologist teams for many years, notably on chemistry-based protein modification strategy for endocytic pathway leading to one of the aforementioned publications (*Nature*) but also to articles in *Angew Chem Int Ed Engl* (1) and *ChemMedChem* (1).

Assessment of the unit's academic reputation and appeal

All teams attract students, post-docs from France and other countries and are well funded by institutional and industrial funds (ANR, INCa,). Team 1 leader was recently elected EMBO member, a prestigious academia in Europe. Two talented young researchers were hired as researchers.

Assessment of the unit's interaction with the social, economic and cultural environment

The committee did not notice any weakness on this point. This is remarkable because excellence in basic research does not necessarily imply strong involvement in other aspects of scientific life. Among the most noticeable points: 1) Translational research is highly developed (up to the creation of two start-up companies). 2) Researchers support an important chemical library accessible to the community. 3) Teaching is frequent despite the fact that the unit is not associated with a university (two PIs teach about 40 to 60 hrs/year and are involved in courses organization). 4) Researchers are highly involved in international and national committees or jury work (NSF, ERC, ANR, AERES, CNRS and INSERM sections, INSA, Collège de France, Ligue contre le cancer), in journal editorial boards (Plos One, Amer. J. of Physiol., Traffic,...) as well as in scholarly associations (Société de Chimie Thérapeutique, Société Française de Chimie, Fédération Réaumur, Club Endo Exo...).

Assessment of the unit's organisation and life

The new Unit will be quite small, hence facilitating governance. In addition, Team 1 leader and Team 2 leader (who was formerly Team 1 co-leader) have already shown their ability to combine their strengths in a successful manner. Lab meetings and retreats are scheduled. Resources will be shared. One PhD students has Team 1 and Team 3 leaders as co-supervisors. These two later facts are very positive signs of collective ambitions.

Assessment of the unit's involvement in training through research

With 6 thesis defenses in the current biology teams (5 affiliated to the Ecoles doctorales ED 419 Signaling and Integrated Networks in Biology of Paris 11 University, 1 to the ED 474 "Interdisciplinaire Européenne Frontières du Vivant" of the PRES Sorbonne Paris Cité (Paris 5 and 7 Universities) and 6 thesis defenses in the chemistry unit (5 affiliated to the ED 436 “Médicament, Toxicologie, Chimie, Environnement” of Paris 5 University and 1 to the ED 388 "Chimie physique et chimie analytique de Paris Centre" of Paris 6 University), there is a good tradition of training through research on both sides. All the PhD students were further followed by thesis committees that met every 18 months. Moreover, they have all the possibility to attend conferences for presenting their work. In addition, the PIs give lectures in national and international courses and seem very active in teaching, notably in the Paris area.

Assessment of the five-year plan and strategy

The creation of the Unit anticipates changes in human resources in the former chemistry Team 3 (moves and retirements). To capitalize the expertise of this team in medicinal chemistry and to stimulate new lines of research, the idea is to gather within a single research unit both chemists of this former group around the next Team leader and biologists around Team 1 and 2 leaders. These scientists have shown great interest and success in translational research, notably in chemical biology, beyond their outstanding works in cell biology.

The creation of the unit will not be in phase with the setting-up of a single new location for all research groups. Instead, the researchers will remain in their current lab and workspaces, although some short-term changes are proposed to mix part of the biologists and chemists in shared spaces and to improve the size of existing bench rooms. Large scale operations involving not only the Institut Curie but also universities and engineering schools/higher training institutions within and outside Paris will determine the various possibilities for a unique lab space. Therefore, the creation of this research unit anticipates changes in the area of Paris, where space is seldom. Delays for these interdependent operations are difficult to anticipate and are unlikely to lead to rapid changes within the next two years.

Overall, the strategy seems both rational and ambitious: to target well defined opportunities suggested by new research lines and successful and talented PIs to build, despite uncertainties linked to other operations at a larger scale, something new within an Institute where collaborations across different fields are a tradition.

4 • Team-by-team analysis

Team 1 : Endocytose et délivrance thérapeutique

Name of team leader: Mr Ludger JOHANNES

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions			
N2: Permanent EPST or EPIC researchers and similar positions	3	2	2
N3: Other permanent staff (without research duties)	3 [2,3]	2	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	7	7	
N6: Other contractual staff (without research duties)	2	2	
TOTAL N1 to N6	**15** [14,3]	**13**	**2**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	5	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit	12	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	3	2

• Detailed assessments

Assessment of scientific quality and outputs

The Team 1 leader is an internationally recognized leader in the field of endocytosis and membrane trafficking. He has been heading an independent research group focused on clathrin-independent endocytosis since 2001 in the UMR 144 (director B GOUD at the Institut Curie. Throughout his career and particularly during recent years, his scientific output has been remarkable both from a quantitative and qualitative point of view. Team 2 leader contributed to these impressive works.

As a whole, the former team (1 & 2) has published 70 original papers between 2007 and 2012 including 4 research papers and 2 reviews in top journals (*Nature* and *Cell*). Team leader 1 was corresponding author of one research article in *Nature*, two research articles in *Cell*, and two reviews in *Cell*. Those papers, even the most recent ones, are already highly cited.

The former team (1 & 2) has uncovered new molecular mechanisms in membrane trafficking and mechanics:

- In 2007, they showed that membrane deformation during Shiga-toxin uptake, which occurs independently of clathrin, takes advantage of the clustering of glycolipids in the outer leaflet of the membrane. Membrane deformation is thus imposed by the cargo from the outside of the cell and not by a cytosolic 'coat' protein from the inside. In 2010, they demonstrated a similar mechanism for the uptake of SV40 virus in collaboration with A HELENIUS (Zurich). These new mechanisms of cell entry are probably not limited to cell invasion by pathogens. Rather, they might illuminate more general endocytotic pathways, which are functionally very important although their molecular basis has remained obscure. A recent work on an endogenous extracellular lectin (galectin-3) that can mediate glycolipids clustering for its own uptake supports this hypothesis.

- After having studied membrane deformation, the group moved to membrane fission and described in 2010 a novel mechanism of dynamin-independent membrane scission via the involvement of actin and line tension. This work highlights the excellent internal collaborations in the Institut Curie between biologists and physicists.

- Recently, they published a remarkable article on caveolae that challenges the classical view on the function of those small structures decorating the plasma membrane (see report on Team 2).

Not only are the aforementioned studies important for our understanding of cellular membranes but also they trigger new lines of research with important biomedical implications. Thus, the group has performed two noticeable studies in this area, including:

- A high-throughput screening to identify small molecule inhibitors that protect cells from ricin and Shiga-like toxins

- Novel Shiga-toxin derived adjuvants for the induction of specific T cell responses as vaccine development.

Assessment of the team's academic reputation and appeal

The work from the team has been internationally recognized at the highest level. Team 1 leader has been invited to 35 conferences during the period of 2007 to 2012 including prestigious events such as Gordon conferences, EMBO, ASCB, FASEB, Naito etc... He has lectured during the same time period at 39 leading international research institutions, such as the ETHZ, Yale, the NIH, just to name a few. He has himself organized a number of important conferences, like the EMBO endocytosis meeting. His achievements have been recognized through the election as EMBO member and through an INSERM-clinical interface contract.

Team 1 leader has been heavily involved in the evaluation of research through committee work in CoNRS/INSERM recruitment/evaluation commission (INSERM CSS3, CoNRS 23). Further, he has worked on editorial boards of leading journals, as editors and as referees for leading journals and agencies. He has also participated in AERES evaluation committees.

Last, numerous collaborations exist with excellent groups in the Institut Curie, in France and within the world and two chargés de recherche have been hired over the last years. The group is well funded by grants from national and international organization (ANR, HFSP...). The excellent reputation and appeal of Team 1 leader is further indicated by his direct supervision of 6 post-docs, most coming from abroad.

Assessment of the team's interaction with the social, economic and cultural environment

Team 1 leader has established two companies during the recent years. This has been possible through the filing of 7 patents and has created several jobs in France and in other countries. The products developed in these companies are promising for cancer therapy and clinical trials for the treatment of breast cancer are underway. Furthermore, the group is member of the LabEx CellTisPhyBio.

Assessment of the team's organisation and life

The former team (1 & 2) has an excellent organization bringing together scientists from different fields of expertise, including staff with medical background. Lab meetings are held regularly, progress is discussed continuously. Team leader and co-leader have previously worked in very synergistic manner.

Assessment of the team's involvement in training through research

The team belongs to the Ecole Doctorale ED 419 Signaling and Integrated Networks in Biology of Paris 11 University. Of the 11 PhD students, which have been trained by the former team, Team 1 leader has supervised 5 PhD students (3 have defended), 3 from foreign countries (USA, India, Germany). One of these 3 PhD students was further affiliated to the ED 474 "Interdisciplinaire Européenne Frontières du Vivant" of the PRES Sorbonne Paris Cité (Paris 5 and 7 Universities). For those of them who already defended, they had a very strong scientific output and went on to a successful scientific career (in companies or as post-docs in excellent labs in France or abroad: EU-openscreen, Biozentrum, Columbia).

The Team head has been involved in teaching/organizing events and courses at the national and international level for a very substantial amount of time (> 40 hrs/yr).

Assessment of the five-year plan and strategy

Given previous successes, the proposed directions make a lot of sense. There is a good balance between risky lines and continuation of previous works. Trying to dissect the code between extracellular cargoes and glycosphingolipids for their mutual interaction is very challenging but the team seems to have the shoulders for such a large scale project. Antigen cross-presentation is fascinating process whose molecular basis is poorly understood; the role of domain boundary forces in this mechanism is an interesting and original hypothesis. Last, deciphering the molecular machineries involved in early endosomes to TGN transport should interest many experts in membrane traffic.

Conclusion

- Strengths and opportunities:

Almost all previous findings of the lab contribute to strengths and opportunities as they are quite unique and suggest new lines of research and applications. To quote a few, the recent finding that extracellular galectins (an endogenous exocytosed ligand) follow the same general mechanism of cell entry as Shiga Toxin, suggests that the mechanisms previously uncovered by the team have a broad implication, i.e. there are not limited to the 'exotic' case of a few toxins.

- Weaknesses and threats:

There exist so many lipids and notably glycosphingolipids in the external leaflet of the cell that uncovering the 'carbohydrate code' is very challenging. However, the committee thinks that the team has the shoulder to address this large issue, notably in this new 'chemical biology' unit.

Another very challenging but exciting issue is protein translocation across endosomal membranes.

- Recommendations:

The group is simply encouraged to continue its superb work.

Team 2 : Dynamique et Mécanique Membranaires de la Signalisation Intracellulaire

Name of team leader: Mr Christophe LAMAZE

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions			
N2: Permanent EPST or EPIC researchers and similar positions		1	1
N3: Other permanent staff (without research duties)			
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		4	
N6: Other contractual staff (without research duties)		1	
TOTAL N1 to N6		**6**	**1**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students		
Theses defended		
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions		1

• Detailed assessments

Assessment of scientific quality and outputs

The discovery that caveolae act as tension sensors is a breakthrough in cell biology and should have a strong impact in the future. The original work was published in Cell in 2011 and is already cited 30 times. Team 2 leader was co-corresponding author of this paper and then published a review on this topic with his collaborator in physics in one of the best review journal (Trend in Cell Biology). Because of their shape, caveolae have been proposed to be intermediates in endocytic pathways (40 years ago, Simionescu and Palade suggested that they are involved in the trans endothelial transport of Albumin). Instead, this new study demonstrates that caveolae act as mechanosensors at the plasma membrane, serving as membrane reservoirs for cells that experience sudden and acute mechanical stress.

Besides this most important and original study, Team 2 has published papers on other research lines (endocytosis, sterol transport…) and in more specialized journals (1 FASEB J, 1 JBC, 1 PLoS one, 1 FEBS Lett, 1 Cell Microbiol) where the PI is a co-corresponding author. Team 2 leader also contributed to many of the spectacular papers on clathrin-independent endocytosis (e.g. Shiga Toxin) published with Team 1.

Assessment of the team's academic reputation and appeal

The Team 2 leader is well known at the international level for his previous works on clathrin—dependent and -independent endocytosis as well as for the interplay between membrane compartmentalization and signal transduction. His recent finding on caveolae and mechanotransduction should further increase his visibility. During the last 5 years, he was invited to talk in 12 conferences including ASCB, EMBO endocytosis and in well-known universities in Europe and North America. He has organized important national conferences, such as the Fédération Réaumur des Sciences du Vivant or the Exo-Endo Club. The team is well supported by funds from ANR. With 6 post-docs, four from France, two from India, the team is very attractive.

Assessment of the team's interaction with the social, economic and cultural environment

The team leader has strong implication in scientific animation: first in committees for French fundations and agencies (ANR and AERES, INSERM CSS); second as an academic editor for PLoS ONE; last as an organizer of conferences in France (Congrès Réaumur). He also has been a co-founder of the exo/endo club that plays an important role in the field of cell biology in France and he is involved in translational research through a joint programm with the Swiss biotech NovImmune.

Assessment of the team's involvement in training through research

The Team leader is highly involved in training and teaching (about 50 hours/yr), largely above the average for a CNRS or INSERM researcher. The team is affiliated to the Ecole Doctorale ED 419 Signaling and Integrated Networks in Biology of Paris 11 University, and has trained 5 PhD students (3 have defended, all with publications), three from France, one from Germany and one from Poland.

Assessment of the five-year plan and strategy

The committee was impressed by the oral presentation and responses during the discussion. Team 2 leader showed an excellent and fair self-evaluation as well as a deep knowledge of many issues in cell biology. On the one hand, Team 2 leader is aware that his recent finding on caveolae is a turning point and a fantastic opportunity to build something new. On the other hand, he considers that mechanotransduction remains a special field where other expertise is needed and that he has to keep a niche at the crossroads between signal transduction/traffic and caveolae. His relationship with Team leader 1 is very good and constructive and this should help building the new unit.

Conclusion:

● Strengths and opportunities:

As mentioned above, the opportunity is obvious and most exciting: the seminal finding that caveolae act in mechanotransduction should trigger new lines of investigations. The committee also noted that these structures, by their shape, unusual lipid composition, original protein topologies (e.g. amphiphilic character of caveolin) are interesting from the physicochemical point of view and could be inspiring for the chemists to build specific probes that may help to follow membrane tension. This fits well with the objectives of the new unit.

● Weaknesses and threats:

The team will have to balance the efforts between what is new (caveolae and mechanotransduction) and the more classical lines of research (traffic and signal transduction) in a small team with only one tenure researcher.

● Recommendations:

The committee simply advises the team to continue its effort on caveolae and to discuss opportunities with chemists to probe caveolae local environment as a function of mechanical stress. Of course, securing some positions will help to give stable grounds to the team.

Team 3 : Chimie des biomolécules, des sondes, et des inhibiteurs hétérocycliques

Name of team leader: Bilan : Mr Jean-Claude FLORENT

Projet : Mr Frédéric SCHMIDT

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions			
N2: Permanent EPST or EPIC researchers and similar positions	4	3	3
N3: Other permanent staff (without research duties)	4 [3,5]	3	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	2	1
N6: Other contractual staff (without research duties)		1	
TOTAL N1 to N6	**10** [9,5]	**9**	**4**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	4	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit	5	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	5	4

• Detailed assessments

Assessment of scientific quality and outputs

Team 3 has a very good track record of publications (39) within the period of evaluation. Some papers were published in top journals (2 Angew Chem, 2 Cancer Res, 5 J Org Chem, 2 Faseb, 1 Nature). The most prestigious publications were generally the results of collaborative studies with biologists from the Curie Institute. As such, the chemists did not always appear as the principal authors in several important publications.

Among the milestones of the last years, three lines of research at the interface between chemistry and biology should be highlighted: (1) Vectorization based on Shiga Toxin of antitumor compounds and contrast agents. These works are associated to proofs of concept for a topo-isomerase inhibitor and for apoptotic drugs. (2) Chemical Biology: biological molecules have been modified and the chemical library of the Curie Institute has been developed leading to the discovery of inhibitors for syndecan-1 and protein kinase CK2. (3) Chemistry: the team has successfully developed self-immolative spacers in which a drug and a probe can be released with predictable and tunable rates.

Assessment of the team's academic reputation and appeal

The work of this team fits very well with current issues at the interface between biology and chemistry. The researchers have developed a large network of collaborations in France notably within the Curie Institute. Overall, this has lead to a number of projects supported by the ANR (4), INCA (3), PIC (2) and Innabiosanté. Six post-docs have been hired. International collaborations are more seldom as well as participations/invitations to international events.

Assessment of the team's interaction with the social, economic and cultural environment

The team has been very active in technology development and transfer with 6 patents (including two licences). The labeling 'Institut Carnot' of the Institut Curie acknowledges these efforts to develop translational research and applications. Some researchers belong to the science advisory boards of companies. Also noticeable is the primary role of the team in the chemical library of the Institut Curie, a very valuable tool for the community. The Team leader is involved in the Société de Chimie Thérapeutique.

Assessment of the team's organisation and life

Given the retirement and moves, this aspect is difficult to assess. However, Team 3 has been very active in setting up the chemical library of the Institut Curie. They have organized lectures, short workshops (journées de la chimie organique et chimie biologique) and an international conference (Rencontre Internationale de Chimie Thérapeutique). Their active collaborations within the Curie Institute show a good integration. This integration is perhaps at the expense of the influence of the team in chemistry: collaborative works with biologists sometimes hide the merits of the chemists. However, this imbalance is a general trend given the growing importance of biology and the fact that many biological issues are inspiring for chemists but can hardly be attacked solely by them.

Assessment of the unit's involvement in training through research

The team belongs mostly to the Ecole Doctorale ED 436 "Médicament, Toxicologie, Chimie, Environnement" of Paris 5 University. With 10 PhD students (6 have defended), all with publications, and with lectures at Master 1 and 2 levels, the team shows a marked involvement in training and teaching. One ongoing PhD student is affiliated to the ED 388 "Chimie physique et chimie analytique de Paris Centre" of Paris 6 University.

Assessment of the five-year plan and strategy

Among the four lines of research, two are extremely innovative: vectorization based on Shiga Toxin and self-immolative spacers. In both cases the team is in excellent position to develop these topics given its expertise, its previous works and because of the reorganization of the unit with the experts in biology. The challenge will be to keep some independence notably through other projects, which should have been better detailed, and, as such, to balance the merits between the teams in biology and in chemistry. In this respect and as previously detailed in the general comments, the committee thinks that the membrane structures studied by Teams 1 and 2 could be inspiring for probe developments given the fact that these structures have peculiar composition asymmetry, curvature…

Conclusion

● Strengths and opportunities:

This new unit in 'chemical biology' is a very good opportunity for the Team's 3 chemists to develop researches at the interface between their field and biology. The reasons are obvious: the excellence of the research, the novelty of the biological mechanisms, their potential impacts in drug design and vectorization, and the ongoing collaborations between the researchers.

● Weaknesses and threats:

The visibility is modest at the international level. The team size decreases as a consequence of moves and retirements. For the moment the partnership with the biologists is chemistry *for* biology not chemistry *with* biology.

● Recommendations:

On a short term basis, the team should put the emphasis on what has been successful with the biologists over the last years.

On a long term basis, the team should put a great deal of efforts into a deep understanding of the processes studied by the biologists. Despite their complexities, the committee thinks that these mechanisms are sufficiently new to inspire innovative organic chemistry approaches; in brief, the plasma membrane is a puzzle of domains whose dynamics, structure, polarity, mechanics are extremely difficult to study with the current tools.

The team should be more active at the international level (attendance to conferences abroad).

5 • Conduct of the visit

Visit date:

Start:	Tuesday, 13 November 2012 at 8h15
End:	Tuesday, 13 November 2012 at 18h00

Visit site:

Institution:	Institut Curie
Address:	26, rue d'Ulm, 75248 Paris Cedex 05

Conduct or programme of visit:

8h15-8h30	Accueil par Mr. Daniel LOUVARD, Directeur du Centre de Recherche de l'Institut Curie
8h30-8h45	Présentation de l'AERES par le Délégué AERES au Comité de visite (huis clos)
8h45-9h	Présentation du Comité et de l'AERES par le Délégué AERES devant l'unité
9h-10h	Présentation générale de l'unité par les directeurs actuel (bilan) et proposé (projet) et discussion
10h-10h45	Bilan et projet Equipe Endocytose et Ciblage Thérapeutique (Mr Ludger JOHANNES)
11h-11h40	Projet Equipe Dynamique et Mécanique Membranaires de la Signalisation Intracellulaire (M. Christophe LAMAZE)
11h40-12h30	Bilan et projet Equipe Chimie des biomolécules, des sondes, et des inhibiteurs hétérocycliques (Mr J.-C. FLORENT/Mr F. SCHMIDT)
12h30-13h :	Rencontre avec les représentants des Tutelles (CNRS+ INSERM+Institut Curie) – Auditoire: membres du Comité, Délégué AERES
14h-14h20	Rencontre avec les ITA titulaires et CDD – Auditoire: membres du Comité, Délégué AERES, sans les Tutelles, ni la Direction
14h20-14h45	Rencontre avec les doctorants, post-doctorants et/ou CDD « chercheurs » Auditoire : membres du Comité, Délégué AERES, sans les Tutelles, ni la Direction
14h45-15h15	Rencontre avec les chercheurs titulaires - Auditoire : membres du Comité, Délégué AERES, sans les Tutelles, ni la Direction, ni les chefs d'équipe
15h15-15h30	Débriefing – Présence: membres du Comité, Délégué AERES
15h30-16h00	Rencontre avec les chefs d'équipe puis la direction de l'unité, le cas échéant (optionnel, à la demande du comité) – Auditoire: membres du Comité, Délégué AERES
16h00-18h00	Réunion du comité à huis clos - Présence : membres du Comité, délégué AERES

6 • Statistics by field: SVE on 10/06/2013

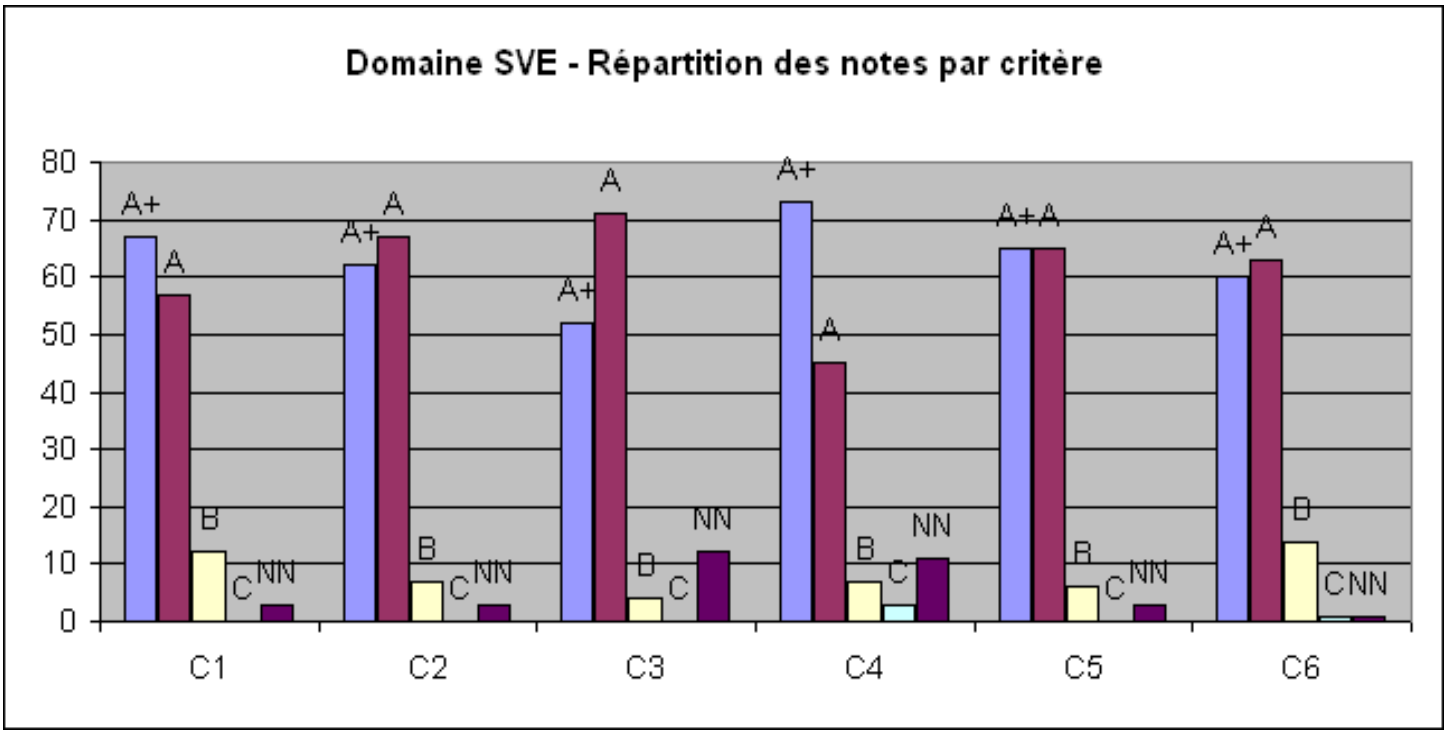
Grades

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	67	62	52	73	65	60
A	57	67	71	45	65	63
B	12	7	4	7	6	14
C	0	0	0	3	0	1
Non Noté	3	3	12	11	3	1

Percentages

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	48%	45%	37%	53%	47%	43%
A	41%	48%	51%	32%	47%	45%
B	9%	5%	3%	5%	4%	10%
C	0%	0%	0%	2%	0%	1%
Non Noté	2%	2%	9%	8%	2%	1%

Histogram



7 • Supervising bodies' general comments

CENTRE DE RECHERCHE

institutCurie
Ensemble, prenons le cancer de vitesse.

AERES
Section des Unités
20, rue Vivienne
75002 PARIS

Paris, le 17 avril 2013

Concerne : Rapport : S2PUR140006128 - Chimie Biologique des Membranes et du Ciblage Thérapeutique - 0753172R – Unité IC/CNRS/INSERM Directeur pressenti : Ludger Johannes

Chers Collègues,

En tant qu'organisme hébergeur et déposant unique des rapports des unités de recherche du site de Paris de l'Institut Curie – Vague D, je vous informe avoir bien reçu en date du 13 janvier 2013, le rapport d'évaluation de l'AERES sur l'unité indiquée en rubrique.

J'ai lu ce document avec attention et vous informe n'avoir aucun commentaire ni remarque à y apporter. Je tiens à saluer le travail réalisé par les experts.

Afin d'assurer le succès continu de cette unité, j'ai bien noté les recommandations du comité pour appuyer ce plan en tenant compte de l'évolution de cette unité et tous les efforts seront faits en coordination avec les tutelles : l'Institut Curie, le CNRS et l'INSERM pour assurer les soutiens nécessaires.

Je tiens à exprimer tous mes remerciements aux membres du comité d'évaluation pour leurs commentaires et recommandations très pertinents qui sont basés sur un travail d'analyse approfondie. Je remercie également l'équipe de l'AERES qui a soutenu la mise en oeuvre de l'ensemble de cette évaluation.

Je vous prie d'accepter, Chers Collègues, mes plus cordiales salutations.

INSTITUT CURIE SECTION RECHERCHE

Daniel LOUVARD
Directeur de la Section de Recherche
INSTITUT CURIE

26 rue d'Ulm - 75248 Paris Cedex 05
Tél. 33 (0)1 56 24 55 00 - www.curie.fr