IBBMC - Institut de biochimie et biophysique moléculaire et cellulaire

Rapport Hcéres

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

Section des Unités de recherche

Evaluation report

Research unit :

Institut de Biochimie et Biophysique Moléculaire et Cellulaire

of the University Paris 11

February 2009

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et de l'enseignement supérieur

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Evaluation report

Research unit :

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of the University Paris 11

Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

February 2009

Evaluation report

The research unit :

Name of the research unit : Institut de Biochimie et Biophysique Moléculaire et Cellulaire

Requested label : UMR CNRS

N° in case of renewal : UMR 8619

Head of the research unit : M. Lucienne LETELLIER

University or school:

University Paris 11

Other institutions and research organization:

CNRS

Dates of the visit :

November 26th 27th 2008

Members of the visiting committee

Chairman of the commitee :

Ms. Cécile WANDERSMAN, University of Paris 7

Other committee members :

M. Dominique BELIN, University of Geneva

M. Simon FOSTER, University of Sheffield

M. Patrice GOUET, University of Lyon 1

M. Philippe MARIN, University of Montpellier

M. Daniel PICOT, University of Paris 7

M. Mathieu ARLAT, University of Toulouse

M. Marc DELARUE, University of Paris 6 and Paris 7

M. Michel RECORD, University of Toulouse

M. Philippe BENAS, University of Paris 5

CNU, CoNRS, CSS INSERM, représentant INRA, INRIA, IRD.....) representatives :

Mrs Françoise SCHOENTGEN, CoNRS representative

Observers

AERES scientific representative :

M. Thierry RABILLOUD

University or school representative :

M. Michael DUBOW, University of Paris 11

Research organization representative :

M. Thierry MEINNEL, DSA CNRS

1 • Short presentation of the research unit

- Number of researchers with teaching duties : 26
- Number of full time researchers : 22
- Number of postdoctoral fellows : 11
- Number of PhD students :20, all with funding
- Number of engineers, technicians and administrative assistants : 15
- Numbers of HDR :33
- Numbers of students who have obtained their PhD during the past 4 years :16
- Average length of a PhD during the past 4 years :3.9 years
- Numbers of "publishing" lab members 40 out of 48

2 • Preparation and execution of the visit

The visit was well prepared. All members of the review panel got before the site visit the necessary scientific and administrative documents for a proper evaluation of the scientific activity of the Unit and its project.

The site visit was well organized, and enough time was allocated for all subheadings of the visit. After the scientific presentations made by the director of the research unit, the expert review panel could meet the representative of Paris 11 University and CNRS. The committe split to meet the different staff categories: researchers, PhD students, technicians and administrators, and the split configuration was kept to visit each research team and thus allocate enough time to go into the details of the science and of the projects.

3 • Overall appreciation of the activity of the research unit, of its links with local, national and international partners

The IBBMC institute has 3 major scientific themes : i) protein structure function and dynamics, ii) bacterial envelope and host-pathogen interactions and iii) cellular communications.

It comprises more than 70 people and is structured in 14 research teams, but one of the teams will leave and two will merge with existing ones (see next section).

The overall scientific production has been very positively appreciated by the review panel, although the quality varies between teams from good to excellent (see next section). A good national and international renown of the laboratory in its specific fields, with good publication citation rates, has also been acknowledged.

Competitive grants (ANR, EU) have also been obtained by several teams, which further testifies the quality and interest of the research, as well as their insertion into international networks (as shown by the EU grants). Some teams also have industrial collaborations, while some others have shown activities oriented to the large public audience. These side activities have by no means altered the core scientific activity of the unit.

Several important changes are scheduled for the coming four-years contract. First of all, the current vice-director will become director next year, and the committee recommends that the research team headed by the future director shall be strengthened. Second, the cellular communication theme will be strongly reorganized. There will be team merges, which will reduce the number of teams from the current 5 to 3. The review panel sees these changes very positively, as this should result into more powerful teams.

4 • Specific appreciation team by team and/or project by project

Axis-1 Protein structure dynamic and function

Team 1a

The Small Angle X-ray Scattering (SAXS) team is a recent (arrived in 2004) and valuable addition to the Institute. The method allows to determine the low resolution shape of macromolecules and their complexes in solution and is complementary to other structural methods used in the Institute. The team has a brand new in-house X-ray equipment and has regular access to the new synchrotron SOLEIL SAXS beamline (only 5mn-drive away from the lab). Indeed, the team has excellent collaborations with other groups in the Institute, especially the Macromolecular Crystallography group and also on campus (e.g. the Laboratoire de Physique du Solide in Orsay). Other collaborations involve viral proteins both in Gif/Yvette (CNRS) and in the Pasteur Institute, Paris. A new emergent and promising theme concerns the structure of large nucleic acids (especially RNA) in solution. The leader is very well connected to the SAXS international community, especially the Svergun group in EMBL Hamburg and is regularly invited to International conferences, practical schools and workshops. The level of publications is excellent; the expertise of the group is unique in France and should be encouraged. The group should consider the possibility to hire a joint post-doc and/or PhD student together with the crystallography group.

Nom de l'équipe : Diffusion des rayons x aux petits angles

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	A	A

Team 1-b

The group working on protein design and engineering (also with methods derived from directed evolution) has a very interesting project trying to combine and mix both an experimental and a computational approach. On the experimental side, the work using neocarzinostatin as a structural platform has given several interesting results. The group has also started to work with repeat proteins, following the method of A. Pluckthun. The aim is to develop new functions by taking advantage of the combinatory of these constructs. Only preliminary results are available at this stage. The head of the lab has a proven expertise in micro-calorimetry, leading to several collaborations. We note that about half of the publications of the lab are in fact due to external collaborations. The team recently got several ANR grants, in collaboration with other labs. The team in charge of computation and modelling is very productive both in detailed applications and in developping new methods. However, we note that i) most of its projects are not really centered on protein design and/or helping to shape/direct protein design experiments and ii) it is under-represented compared to the size of the group performing the experiments. Therefore, it would be advisable to hire at least one person to replace the leaving CR1, together with one post-doc or student, so as to balance the workforce in the two aspects of protein design and make the overall project more coherent/competitive with the ones of other international groups. Finally, we note that the group appears on the overall somewhat fragile with respect to inevitable fluxes of personal (post-docs, PhD students) as well as to the many duties of the people with a teaching position. As the head of the lab will take the responsibility of the whole Institute, and still has many outside collaborations (including serving as a consultant for the industry), the committee is concerned that there might be a succession problem in the day-to-day operations management of this lab. The committee has no detailed solution to this potential problem but wishes nevertheless to point it out to the attention of the managers.

Nom de l'équipe : Modélisation et ingénierie des protéines

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	B	B

Team 1-c

The structural genomics group was created in 2001. Since then, it has acquired an international reputation with a total of 80 publications in highly ranked journals and numerous participations in major European programs of structural genomics (SPINE, SPINE2, 3D Repertoire, VIZIER, BIOXHIT). The team has 20 members and includes eight senior scientists distributed equally between CNRS and University. From 2001 to 2005, the team worked on yeast proteins, adopting a "rough" structural genomics approach. It set up a platform for protein purification and crystallization opened to the scientific community, which obtained the RIO label in 2003. The group redefined its objectives in 2005 (end of the yeast pilot project) and started working on protein complexes. This research on protein-protein and protein-ligand interactions covers a wide range of relevant biological subjects (eukaryotic mRNA quality control pathway, bacterial competence, telomere maintenance, extracellular matrix proteins, viruses infecting hyperthermophilic archae) and is supported by three European and seven French grants (SPINE2 for complexes involved in signalling pathways involved in human health and disease., 3D Repertoire for yeast protein complexes, VIZIER for RNA viruses, ANR for mRNA decay, "Mutabilis" -a biopharma company- for anti-bacterial drugs, …). Research benefits from the modern technology of the RIO platform (e.g. the nanodrop crystallisation robot) and from the expertise of the group in bioinformatics (e.g. the group is strongly involved in the program CAPRI, Critical Assessment of Prediction of Interactions). Such reorientation of the research objectives of the team required reorganization. Projects are now selected according to their biological interests and are directed by a single senior scientist. Moreover, to keep the scientific consistency of the team, several projects have been chosen according to the results obtained within the yeast structural genomics pilot-project (program 3D repertoire). The committee approves this evolution allowing a scientist to take a greater interest in his research. He congratulates the team for the quality of its publications during this four-year (58 articles in total, 35 articles with a member of the team as first or last author in leading scientific journals such as JMB, JBC, EMBO J., NAR, Mol Cell,.). The committee appreciates also the implication of the team in the university education program (participation in the research and professional LMD, implication in the doctoral school). The scientific projects pursued by the team in X-ray crystallography and bioinformatics are of quality (BioRib on the biogenesis of ribosomes, fibronectin, mRNa decay, classification of binding sites in proteins…) and collaborations within the IBBMC are under way (an ANR project on the biosynthesis of the peptidoglycan has just started). However, the committee notes that the departures of two senior scientists (one of them to gain a professorship at the University of Paris 5) can affect the level of publication of the team if they are not replaced. Finally, the committee strongly appreciates the strong ties already established between the SAXS team and the structural genomics group. The SAXS technique can now be used in situ for the determination of the low resolution envelope of the complexes. The two teams have started a partnership on the complex KEOPS and on the NMD pathway in yeast. It is worth mentioning that these two teams and several others at the IBBMC are lacking an engineer in charge of informatics, bioinformatics upgrades and data storage.

Nom de l'équipe : Génomique structurale

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	A	A

Team 1-d

The team « dynamics of proteins and membranes interfaces » specialises in time-resolved fluorescence to study proteins-membranes interactions and membranes interfaces dynamics. During the four last years, in collaboration with researchers from other laboratories, the group studied several topics including : the role of the N-terminal domain of annexins during interaction with membranes; the role and localization of aromatic residues of yeast PMP1 fragments in interaction with detergent micelles; the structure and dynamics of human Multidrug Resistance Protein (MRP1) fragment 17 in membrane models; the interactions of pyoverdine with Pseudomonas Aeruginosa receptor. Furthermore, the group studied the nanosecond dynamics of a mimicked membrane-water interface by time-resolved stokes shift of Laurdan (a fluorescent probe sensitive to solvent polarity); in these experiments, the dipolar relaxation at the interface membrane-water was measured upon inversed micelles. Considering the few number of workers in this team (only 2 researchers), the scientific production is quite correct (9 publications in journals of high quality). The project of the team is the continuation of the present work, i.e. the study of interactions between peptides and proteins and membranes models such as Small Unilamellar Vesicles (SUV), Large Unilamellar Vesicles (LUV) or micelles. The main research topics will be : 1- the annexin 2 N-terminal domain ; 2- the peptides TM16 and TM17 from human Multidrug Resistance Protein (MRP1) ; 3- the ß amyloid peptides of APP; 4- the Ervinia Carotovora virulence factor. Moreover, in collaboration with a group in Strasbourg, the interaction between siderophores and bacteria membranes will be characterized. The two researchers of the team will stop their scientific activity in 2011 for retirement. It seems desirable that the IBBMC maintains the possibility to study the interactions between membranes and proteins by fluorescence. As a solution, the IBBMC could entrust this task to an engineer in charge of a platform dedicated to several biophysical methods (e.g. steady-state and time-resolved fluorescence spectroscopy, Differential Scanning Calorimetry, etc.).

Nom de l'équipe : Dynamique des protéines et des interfaces membranaires

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
B	B	B	B	B

Axis-2 Bacterial envelopes and host –pathogen interactions

Team 2-a

The assembled team on gram-positive mycocolic membranes is new having only been initiated since the last appraisal. Thus the past period has been spent getting projects started. The team leader has the added duties of teaching at the University, which impinges on his time for research. The publication record is very good, but by necessity has been associated with work prior to the existing appointment. The standard of existing projects is very good establishing new research areas with long-term potential. Already outside funding has been secured, which is a result of its competitive nature. In particular a biochemical approach has been taken, which has resulted in the research group establishing their niche. The model organism chosen provides a useful starting point for relevant studies in pathogens. The transfer to the more important target organisms must be considered a priority in the near future. The proposed research projects are well conceived and will utilize the skills of the research team. The approach is risky, but will undoubtedly establish the research group in the area with a long-term future.

Nom de l'équipe : Microbiologie cellulaire et moléculaire

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	non noté	A

Team 2-b

This group is working on T5 phage infection : a unique model with a sequential DNA injection. The group participated in the T5 DNA sequencing and annotation. This is one of the rare teams working on phage physiology. The team is really interdisciplinary with a physicist starting to work full time on the biology of the system. As a consequence, T5 infection is analyzed using a very large number of methods, from electron microscopy to genetics. The integration of the IBBMC is for instance reflected by the use of SAXS to study DNA encapsidation, while DNA ejection can now be visualized in real time by fluorescence microscopy. This is reflected by a very good number of publications in excellent journals, even though their impact is not superb. The lab has also contributed to an education movie that should encourage young students to move to biology. Actually, the team lacks critical mass as the technician has retired and has not been replaced and the head of the group will retire soon. A competent successor is already working in the group and will take over. However, it is essential that the team is reinforced with new positions.

Nom de l'équipe : Transport membranaire de macromolécules

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	A	A	A

Team 2-c

Peptidoglycan is an essential and specific heteropolymer of bacterial cell walls. As such, its biosynthesis is the target of several antibiotics and it is also one of the main bacterial products recognized by the innate immune system. The biosynthesis of peptidoglycan is a very complex process, involving numerous steps taking place both in the cytoplasm and in the inner membrane. A comprehensive study of the biosynthesis of this major component is therefore necessary to find or design new antibiotic products. Such a work, based on expertise in this specific domain of research, has led to the identification of new enzymes which play a role in this biosynthesis and in particular in the metabolism of undecaprenyl phosphate. Interestingly, these new enzymes might also control the metabolism of other components of the cell envelop, thus having an even more crucial role. The combination of genetic and biochemical approaches which have been developed here is very precious to perform structure/function studies. This work has an impact in enzymology but also in the quest for new inhibitors. It has been carried out with Mur ligases, MraY or MurG, leading to major observations. Moreover, the high quality of these studies is undoubtedly reflected by the participation to European projects and by contracts with private companies. The transposition of knowledge and expertise, gained on the model bacterium Escherichia coli, to the study of peptidoglycan biosynthesis in several pathogenic bacteria is certainly a major new research line which might have an even more important impact. Finally, through very fruitful collaborations, the expertise on peptidoglycan has allowed the characterization of peptidoglycan structural

components recognized by the innate immunity systems of mammals and Drosophila. Peptidoglycan-derived molecules of Gram positive or Gram negative bacteria inducing innate immunity have been characterized and several receptors identified, thus leading to major breakthroughs in this very competitive domain of research. In conclusion this work centered on peptidoglycan biology has made major contributions in several aspects of fundamental and applied biology. It is of top international quality.

Nom de l'équipe : Enveloppes bactériennes et antibiotiques

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A+	A+	A+	A+	A+

Team 2-d

Endotoxins, or LPS, are major constituents of the outer membrane of Gram-negative bacteria. They play a central role in host responses mediated by the innate immune defense. The endotoxin structure group is focusing its activities on the structure of LPS Bordetella, although collaborations have been established to study Pseudomonas and Rhizobia. The group has published six papers in good biochemical or bacteriological Journals, and two more papers as part of collaborations. The group will leave the IBBMC to join another Institute on the Orsay campus. From a letter given to us by the lab members, in the absence of the principal investigator, it appears that the group did not feel integrated enough. This may seem surprising considering that endotoxins should have been of scientific interest to the groups working on bacterial membranes. Although an expertise in lipid biochemistry could have been considered a positive factor for the Institute, it will remain accessible on the campus. Overall, the lab has a reasonable record and may expand its productivity and visibility in its new setting. Future research plans have not been evaluated during this site visit.

Nom de l'équipe : Structure et activités des endotoxines

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
non noté	non noté	non noté	non noté	non noté

Axis 3 Molecular cell communication

Team 3-a

This is a new team, which is the result of a merge of two previously independent teams of the IBBMC, Team "Chimie des Protéines" and Team "Pharmacologie de la Synapse". After the fusion, the team will be composed of four senior scientists (including one "emeritus" professor), two junior researchers and one engineer. Report on previous activities of Team "Chimie des Protéines". During the 4 last years, the team has developed proteomic programs in the fields of microbiology and neurobiology. The first one focuses on the modification of proteome induced by oxidative or heavy metals in photosynthetic micro-organisms and on specific post-translational modifications (glutathionylation) occurring in these conditions. The second one, developed in collaboration with a neurobiologist team, was aimed at identifying modification of protein expression and phosphorylation occurring during late phase of LTP in the dentate

gyrus. This research program is without any doubt important, as LTP maintenance is known to depend on both de novo protein synthesis and phosphorylation events. However, the method used to detect protein phosphorylation (ProQ Diamond) has serious limitations inherent to the lack of specificity of the dye for phosphorylated proteins. In absence of direct assessment of phosphorylated peptides by mass spectrometry, which is a challenge with the facilities available in the team (MALDI-TOF MS), the impact of such experiments is somewhat limited.

The team has also collaborated with another group of the IBBMC to define the proteome of outer membrane enriched in mycolic acids of mycobacteria, which is crucial for the investigation and understanding of transport processes across the mycobacterial cell wall. The overall achievement and production of the team is satisfactory with respect of the heavy teaching duties of most of the staff. Most of the papers, including those signed by the team members as principal investigators, were published in medium to high rank journals such as Proteomics, JBC and PNAS. In terms of external funding, the team has been involved in several national programs and is a partner of two ANR grants.

Report on previous activities of Team "Pharmacologie de la Synapse".

The main research goals of the team are to characterize molecular and cellular mechanisms involved in glutamatergic synaptic transmission and synaptic plasticity in rodent cerebellum (synapses between parallel fibres and Purkinje cells). The team focuses on pre-synaptic control of glutamate release by various G protein-coupled receptors (mGlu4, cannabinoid CB1 and A1 adenosine receptors) and on the control of synaptic transmission by P2X7 receptors expressed on Bergmann glial cells. These projects are very timely and well articulated and the objectives are generally well focused. The team has a long-standing expertise (probably unique in France) of synaptic transmission in the cerebellum and has produced important achievement in the field during the past years. The approaches used are mainly based on a combination of electrophysiological recordings and Ca2+ imaging in acute slices of cerebellum, allowing accurate measurement of changes in Ca2+ concentration at the presynaptic level. Again, this technical expertise is probably unique in France. The overall publication list of the team is satisfactory with most of the papers published in good journals with respectable reputation in this research field (J Neurochem, J Physiol, Neuroscience and J Neurophysiol). The global publication level should greatly benefit in the coming years from the development of complementary approaches, such as proteomics or cell biology and electrophysiology on neuronal cultures, within the new partnerships initiated by the team. Moreover, the productivity of the team will probably be strengthened by the recent integration of two junior scientists.

With regard to external funding, the team has been quite successful. This includes a FRM grant (2005), which allowed implementation and/or upgrade of electrophysiology set-ups and an ANR grant (2007) coordinated by the team leader. Finally, the Committee wishes to point out the very strong implication of the team leader in teaching (master modules, agregation…) as well as in administrative tasks at Paris 11 University.

Nom de l'équipe : Pharmacologie de la synapse

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	B	A	A

Report on the project of the merged team:

The Committee entirely approves the merging of the teams, which is justified by 1) their complementary expertise in biochemistry and proteomics (Chimie des Protéines Team) and pharmacology and electrophysiology (Pharmacologie de la Synapse Team); 2) the strong implication of the Chimie des Protéines Team in Neuroproteomic programs in the past years and 3) the existence of a common project (supported by an ANR contract) aimed at identifying protein network interacting with mGlu4 receptors and controlling glutamate release by parallel fibres. In spite of this merging, the proteomic staff of the team will also pursue proteomic projects in other fields, especially those initiated in collaboration with other teams of the IBBMC. Although there is no doubt concerning the relevance and feasibility of the project on mGlu4 receptor-interacting proteins with regard of the overall program of the team, the Committee

strongly recommends the team to prioritize, at least in the beginning, one or two methods to isolate mGlu4 receptor interacting partners, which have been successively employed to identify protein partners of other membrane-bound receptors: 1) co-immunoprecipitation of partners with native receptors, providing that they obtain a "good" antibody and 2) peptide-affinity chromatography using a synthetic peptide corresponding to the receptor's C-terminal domain, as this domain is the major one involved in GPCR-partner interactions so far identified. The Committee also strongly encourages the proteomic staff to use external mass spectrometry facilities to identify proteins retained by affinity, especially those of the Gif sur Yvette proteomic platform, which includes a last-generation nano-LC-MS/MS system particularly adapted for the high-sensitivity analyses requested by such a program in which the amount of starting material is somewhat limited. Besides this neuroproteomic program, the team will also pursue two previously initiated projects on the modulation of synaptic transmission by P2X7 receptors expressed on Bergman glial cells and on the mechanisms involved in the retrograde control of synaptic transmission. The objectives are generally well defined and in adequacy with the manpower available and the technical expertise of the staff and preliminary data are consistent with the hypotheses. This program should provide important information regarding the mechanisms underlying synaptic plasticity and astrocytic control of synaptic transmission.

Nom de l'équipe : Chimie des protéines

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
B	B	B	B	non noté

Team 3-b

This new team results from the association of two previously independent teams of the IBBMC laboratory, named respectively "Nitrogen oxide, inflammation and Immunity" and "Cell activation and Signal transduction".

Report on previous team "Nitrogen oxide, inflammation and Immunity"

Researches were focused on the role of the inductible NO synthase, one of the 3 enzymes generating the mediator NO, in relation with DNA damages and the regulation of the anti-oncogenic protein p53, as well as its p63 and p73 homologs. Ribonucleotide reductases, which catalyze the reduction of ribonucleotides into deoxyribonucleotides, play a key role in that process by providing dNTPs required for DNA synthesis. It was shown that NO upregulated the p53R2 ribonucleotide reductase. Such enzymes might be involved in resistance to cancer treatments. Data were published in medium (Nitric Oxide) to good rank (Mol.Cancer Ther.) journals, and the principal investigator participated in a high rank publication (EMBO Rep.) in a collaborative work. External fundings were obtained in the frame of a national program related to an antineoplastic agent on p53R2 and P73. The team has without any doubt an excellent expertise of the nitridergic system and of regulation of ribonucleotide reductase system, but its productivity is presently only fair and must be improved in the following years. In this regard, the merging of the team with Team "Activation Cellulaire and Transduction des Signaux" should be very fruitful, due to the established connections between the nitridergic and purinergic systems and their role in both inflammation and cytotoxicity and the expertise of the latter team in signalling mechanisms involved in these processes.

Nom de l'équipe : Oxydes d'azote, inflammation et immunité

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
B	B	B	B	non noté

Report on previous team "Cell activation and Signal transduction"

Activity of this team was focused on immunocompetent cells. The repertoire of T lymphocytes during development of Experimental Autoimmune Encephalomyelitis" (EAE) has been analysed, and it was demonstrated that a diversified T repertoire contributed to aggravation of the disease in animal models. Immunocompetent cells express a particular type of purinergic receptor, which responds to high concentrations of ATP, the P2X7 receptor. The team worked on signalling pathways downstream engagement of P2X7 receptor and leading to thymocyte cell death. Involvement of P2X7 receptor in secretion of some cytokines (IL1 ß, IL18, IL33) whose synthesis was enhanced by LPS was demonstrated. The role of this receptor was also investigated towards NF- κ ß transcription factor activation during survival of lymphocytes B. These works were published in very good journals in the field (J. Immunol., Eur. J. Immunol.) but also in high-ranked generalist ones such as J. Clin. Invest., PNAS or FASEB J. External fundings relied on two national programs related to multiple sclerosis and involvement in a "Marie-Curie Action". Researches encompassed many concepts well assessed by appropriated experimental approaches. All together, it can be stated that this team displayed an excellent expertise in immunocompetent cell signalling.

Nom de l'équipe : Activation cellulaire et transduction des signaux

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	B	A	non noté

Report on the new team "Cellular activation and Signal transduction"

Since several persons from the previous two teams retired or are going to retire, a new team gathering the two expertises was set up. Studies on regulation by iNOS of p53 homologs will be continued but connections with the purinergic receptor P2X7 will be investigated. Experiments are planned with p53 knocked-out mice. Each expertise will be maintained with a recently recruited young researcher in charge of a project making the bridge between the two scientific orientations, i.e investigating the role of P2X7 on iNOS induction with subsequent effect on p73 regulation. NO is also involved in microglia function in the central nervous system in which P2X7 receptors are also expressed. Thus, the project on the role of P2X7 receptors in neurotoxicity will be specifically developed in connection with Alzheimer disease. Activation of this receptor leads to the cleavage by ß and ¥ secretases of APP, the Amyloid Precursor Protein, with subsequent release of the pathogenic ß amyloid peptides. This new scientific orientation on P2X7/ Alzheimer appears to be promising since it is an opened research field, and the team has some reliable preliminary data related to involvement of lipid mediators. This last point could be a way for interactions with the team "Cellular and Molecular Signaling in Uterus". However, the committee suggests the team to consider the role of P2X7 receptor in vesicle-mediated secretion processes of ß amyloid peptides from intracellular compartments since the release of above-mentioned cytokines (IL1 β, IL18) devoid of signal peptides appeared to be

mediated by bioactive vesicles. Interestingly, it has been planned in the project to use P2X7 receptor knocked-out mice and transgenic mice reproducing Alzheimer disease to demonstrate in-vivo the role of this receptor in the disease. To surround its role in humans, the polymorphism of the gene encoding for the P2X7 receptor in comparative healthy and Alzheimer populations will be analysed. The committee is confident on the development of the overall team project, which should provide strong insights in the field.

Team 3-c

The team exhibits a good expertise in cellular signalling related to lipid mediators. The team has analysed signalling pathways downstream endothelin receptors in models of uterine smooth muscle cells. Primary cell cultures from normal mouse uterus or from spontaneous fibrosarcoma (ELT3 cells) developed in mouse were used as cell models. Interest of uterus muscle resides in the different cell phenotypes (proliferation, differentiation, contraction, apoptosis) present at the various physiological stages, allowing to correlate signalling pathways with different cellular responses. Methodological approaches are based on classical tools to analyse signalling pathways: pharmacological agents (enzymatic inhibitors), siRNAs, analysis of protein expression by Western-blotting, measurements of lipolytic activities and lipid kinases. Also cellular contraction as a read-out was measured. The team has also analysed the type of receptor involved upstream the signalling pathways, for understanding how both types of endothelin receptors (ETA and ETB) can cooperate, and how the receptor to the lipid mediator sphingosine-1-phosphate (S1PR) was involved. During the last four years the team has investigated the role of lipid kinases (PI3 kinase, sphingosine kinase) and lipolytic enzymes (phospholipases D, lysophospholipase D [autotoxin]) following engagement of endothelin receptors, and demonstrated the role of lipid mediators such as S1P, PA (phosphatidic acid) and LPA (Lyso-phosphatidic acid) downstream the above-mentioned G protein-coupled receptors. These experiments have been thoroughly conducted and were published in reference journals related to the lipid field (J. Lipid Research), signalling (Cell Signalling), or with pathophysiological scope (Endocrinology). The number of publications was very satisfactory. The research project relies on and extends previous work. The methodological approaches of the team are well mastered, but their expertise would be enhanced by complementary technologies to the ones they currently use. Analysis of receptor dimerisation by FRET would be one of them. The goal would be to analyse more deeply the molecular mechanisms involved for instance in differential signalling between normal and pathological uterine muscle cells, in order to place the lipidic signalling in a more general context. Such a development should allow to publish their results in wider audience journals such as J. Biol. Chem. Collaborations with teams exhibiting complementary signalling knowledge such as that related to NO/COX2 and purinergic receptors (since uterus muscle physiology involves energy [ATP]-dependent mechanisms) would probably boost the lipid mediator expertise of the team. A collaboration with a team in that field within the laboratory has been planned; this collaboration should become preponderant over the other ones also planned. Opening to different technologies and new models including in-vivo ones (a model is proposed in the team project) in interaction with other groups should facilitate success in ANR applications and allow to bring the team research to a stronger international level.

Nom de l'équipe : Signalisation et régulations cellulaires

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
B	B	B	B	B

Team 3-d

The team "prokaryotic ion channels" has a long and well recognized experience in bacterial ion channels implicated in osmoregulation. In particular, it has developed the use of electrophysiological techniques on reconstituted membrane system, this originality has also brought them to acquire expertise in membrane protein biochemistry. It have made important contributions on various channels like MscL, KdgM and PulD. They have also quite early realized

the interest of using in vitro synthesis approaches for membrane protein, and have developed a well recognized expertise that has been used by other communities, like solid state NMR ; they are coordinator of an ANR project to extend this method for other membrane proteins. In particular, they have used fluorinated surfactants (hydrophobic and lipophobic) that allow a direct insertion of membrane proteins into liposomes.

They are now starting new projects on eucaryotic (human and plant) ion channels, and are studying means to apply the in vitro synthesis approach. This extension toward eucaryotic system is welcomed, but very challenging and risky for a small team in a field where large laboratories are now focusing their interests. Therefore, we think that the team should concentrate its strength on questions where it can have a decisive impact and that, on other aspects, it should develop strong collaborations with other laboratories involved in more cellular approaches. They should also not loose they recognized expertise on bacterial ion channels.

Nom de l'équipe : Canaux ioniques des cellules procaryotes

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
B	B	B	B	B

5 •Appreciation of resources and of the life of the research unit

- In terms of management:

The different categories of staff (researchers, students, technicians) considered that the lab was well run by the director and the scientific staff readily stuck to the director scientific strategy. They were also very satisfied by the choice made within the laboratory of a general sharing of the resources (financial, technical, services, weekly internal scientific meetings opened to all the staff). The review panel felt that there was a deep gratitude of the staff for the strong involvement of the director. A very active scientific life at the level of PhD students and postdocs has also been positively appreciated by the review panel. As to the financial resources, they appear satisfactory, with a strong support from the CNRS (examplified by the replacement of the SAXS machine after its damaging by a flooding) as well as resources from external grants.

- In terms of human ressources:

The IBBMC also enjoys a strong proportion of support personnel, as 26 technicians and engineers with a permanent position have contributed to the research of the institute: 17 belong to the CNRS and 9 to the Paris 11 University (UPS).

Like in many French research units, the technical staff is dedicated to support the administration, the common facilities (front desk, technical support, etc…) and the research teams. The administration of the UMR 8619 is helped by 5 CNRS technicians or engineer assistants (AI) and the common technical staff to the research is made of 6 UPS technicians. 15 technical staff members (13 CNRS and 2 UPS employees) are directly involved in the research projects. Indeed 8 technicians, 1 AI, 4 engineers (IE) and 2 research engineers (IR) are involved in the research of numerous teams that represent 48 permanent researchers (23 full time CNRS researchers and 25 Pr or associate Pr) and more than 20 postdoctoral fellows.

The technical staff is spread over numerous teams in an inhomogeneous way, from none up to four technicians per team.

The evaluation committee would like to drive the attention to the imbalanced ratio between the research contributing technical staff and the researcher pool, although this shall be self-regulated by several close retirements among the researchers (but not technicians): for example, 4 research directors out of 11 and 2 full professors out of 7 are more than 60 years old.

In addition, retirement has also impacted the technician staff with 6 departures during the evaluation period, including 3 retirements. In the same period, 2 departures have also been recorded in the technician pool dedicated to administrative tasks.

6 • Recommendations and advice

— **Strong points :**

The evaluation committee outlines the excellent scientific work of this institute and particularly the following strong points:

- High quality and large number of publications in international journals
- Large number of grants such as ANR and EU
- Excellent working atmosphere
- Strong cohesion between students and post-docs from different labs
- Team reorganisation dynamics
- Excellent integration of teaching and research
- Interdisciplinarity with an active interface between biology, chemistry and physics

— **What needs to be improved :**

- A more centralized management for orders, in particular for large equipments
- A better international visibility to be able to attract new teams, a priority not mentioned in the project
- A lack of scientific strategy at medium/ long term
- A better career advice for young scientists and theses committees to follow the progress of graduate students
- A stronger implication of the University in maintaining/renovating the laboratories

— **Recommendations :**

Overall, the review panel has evaluated the scientific activity and project of the Unit as of good quality. It approves the strategy of the Unit to keep its fundamental research specificity at the interface between biology, chemistry and physics. The committee also approves the proposed team fusions to yield bigger and more powerful teams. The change of the IBBMC director which will take place next year should be accompanied by a strengthening of the future director team : a new researcher and/ or teaching discharge for university members.

Note de l'unité	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	B	A	A

UNIVERSITÉ
PARIS-SUD 11

Le Président de l'Université Paris-Sud 11

à

Monsieur Pierre GLORIEUX
Directeur de la section des unités de recherche
AERES
20, rue Vivienne
75002 Paris

Orsay, le 7 avril 2009.

N/Réf. : 105/09/GCo/LM/LS

Objet : Rapport d'évaluation d'unité de recherche
N° S2100012428

Monsieur le Directeur,

Vous m'avez transmis le dix neuf mars dernier, le rapport d'évaluation de l'unité de recherche « Institut de Biochimie et Biophysique Moléculaire et Cellulaire » - IBBMC - UMR 8619, et je vous en remercie.

L'université se réjouit de l'appréciation portée par le Comité sur cette unité et prend bonne note de ses suggestions.

Vous trouverez en annexe les éléments de réponse de madame Lucienne LETELLIER, Directeur de l'unité de recherche.

Je vous prie d'agréer, Monsieur le Directeur, l'expression de ma sincère considération.

Guy COURRAZE
Président

UNIVERSITE PARIS-SUD 11 - Présidence - 91405 ORSAY CEDEX

P.J. : Commentaires de Mme LETELLIER

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INSTITUT DE BIOCHIMIE ET
DE BIOPHYSIQUE MOLÉCULAIRE ET CELLULAIRE
UMR 8619 du Centre National de la Recherche Scientifique

Lucienne LETELLIER - Directrice de Recherche CNRS

Directrice de l'IBBMC

Object: AERES evaluation of the IBBMC, UMR 8619

We would like to thank the AERES committee members for their efforts to provide a helpful evaluation of the IBBMC. The report was sent to all members of the IBBMC. We have read it with great attention and we do agree with almost all items and remarks raised by the committee. We would like to address some specific points raised and to update some information.

As far as the long-term scientific strategy of the IBBMC is concerned, a call for candidature has been published and two scientists/groups are interested in joining soon the IBBMC.

Concerning the strengthening of the teams, we would like to mention that altogether 14 post doct are presently working at the IBBMC and one new assistant professor will be hired on September 2009 to join a recently created team (team 2a). Furthermore, a professor position has been granted in the 2009 campaign. He/she will develop a research project fitting with the scientific IBBMC themes. Finally, a CNRS assistant engineer has been hired beginning 2009 who will strengthen team 2b.

We agree with the committee that we need "a stronger implication of the University in maintaining/renovating the laboratories". This is clearly a *sine qua non* condition for us to attract new teams.

Finally, we appreciate the comment of the committee underlying the good quality of our scientific activity and project. We are also grateful to the committee to have highlighted and supported our scientific specificity to develop projects at the interface between biology, chemistry and physics.

On behalf of the Unit,

Lucienne Letellier

IBBMC director

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M. Michel Desmadril

Orsay, 3rd april 2009

Object : AERES evaluation of the IBBMC UMR 8619

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On behalf of the Unit,

M. Desmadril
IBBMC Vice-Director