LBPA - Laboratoire de biotechnologie et de pharmacologie appliquées

Rapport Hcéres

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

Section des Unités de recherche

Evaluation report

Research unit :

Laboratory of Biotechnology and of Applied Pharmacology

Ecole Normale Supérieure de Cachan

March 2009

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

Section des Unités de recherche

Evaluation report

Research unit :

Laboratory of Biotechnology and of Applied Pharmacology

Ecole Normale Supérieure de Cachan

Le Président de l'AERES	Section des unités de recherche
	Le Directeur
Jean-François Dhainaut	**Pierre Glorieux**

mars 2009

Evaluation report

The research unit :

Name of the research unit : Laboratoire de Biologie et Pharmacologie Appliquée

Requested label : UMR CNRS

N° in case of renewal : 8113

Head of the research unit : M. Jean-François MOUSCADET

University or school :

Ecole Normale Supérieure de Cachan

Other institutions and research organization:

CNRS

Date of the visit :

February 2nd, 2009

Members of the visiting committee

Chairman of the commitee :

M. Jean-Jacques TOULMÉ,University of Bordeaux 2, France

Other committee members :

M. Frédéric BOCCARD,University of Paris 11, France

M. Joachim ENGELS,University of Goethe, Germany

M. Jeffrey HAYES, University of Rochester, NY, USA

M. Yves POMMIER, NIH Bethesda, USA

M. Jean-Louis MERGNY, Muséum National d'Histoire Naturelle, Paris, France

M. Françoise GUERLESQUIN, IMR Laboratory, Marseille , France

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

Ms. Valérie SCHREIBER, CoNRS representative

No representant of CNU.

Observers

AERES scientific representative :

M. Philippe BOUVET

University or school representative :

M. Yves MERINDOL, ENS Cachan

Research organization representative :

M. Thierry MEINNEL, CNRS

1 • Short presentation of the research unit

- Numbers of lab members : 56 including
  - 8 researchers with teaching duties
  - 17 full time researchers
  - 1 invited scientist
  - 5 engineers
  - 15 PhD students
  - 9 technicians, including 4 with temporary positions
  - 1 administrative assistants
- Numbers of HDR: 19
- Numbers of PhD students who have obtained their PhD: 15
- Average lenght of a PhD during the past 4 years: 4 years
- Numbers of lab members who have been granted a PEDR : 1
- Numbers of “publishing” lab members: 24 out of 25

2 • Preparation and execution of the visit

The programme of the visit was established one month ahead in a concerted way between the head of the Unit, the chair of the committee and the AERES representative. The visit itself started by a presentation of both the scientific activity and the re-organisation of the teams by the head of the Unit. Each team leader gave then a 45 mn talk describing his (her) major achievements over the last years and his (her) project for the next 4 years. At lunch time the opportunity was provided to discuss with laboratory members in front of about 10 posters. The committee then visited laboratories and facilities. In the afternoon parallel meetings took place with researchers, technicians and post-docs/PhD students. A door-closed meeting was also organized at the end of the visit.

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

The LBPA (UMR8113 ENS Cachan-CNRS) created in 2002 is an interdisciplinary research unit composed of seven teams (25 researchers and 14 ingenieers/technicians) that remained located on two different sites till 2007. They are now all located on a single site in a brand new building at the ENS Cachan. The LBPA will be reorganized for the forthcoming 4 year contract (see #4 below). Multiple projects (actually too many) are being worked out on a wide range of topics. Those being related to cancer are actually proposed to be continued in the frame of a new independent "service and research" unit (USR) that will be evaluated separately. The activity of the LBPA is strongly technology oriented with an internationally recognized expertise in SPR and in biophotonics, the structural biology team being weaker. On the biological side, the activity of the team working on retroviral replication is excellent and offers an interesting potential for interactions with other groups that should be exploited more.

Members of the LBPA authored over 120 papers, 45 of which published in journals with an IF>5 (1 J Exp Med, 1 Nat Struct Mol Biol, 3 Blood, 4 PNAS, ...). But only 10 of the publications are co-signed by at least two different teams. Five patents have been filled since 2004. Fruitful contacts are in place with the industry, a large part of them connected to the oncology team that is driving the new USR project.

The LBPA is part of the IFR D'Alembert, a federation of laboratories encompassing physics, chemistry, technology and biology. This provides LBPA members with access to shared facilities. However the scientific interaction with other IFR laboratories seems rather weak (only 2 publications co-signed with another team of the IFR out of 120). LBPA researchers are members of international networks with Asia (Vietnam, China, India), Russia and Poland. They contribute to three ongoing EU contracts all of them related to the USR project. Funding is also ensured by 7 ANR grants (in 2008), including 1 "Young Researcher" grant as well as grants from other agencies. This ability to raise EU and ANR funds makes LBPA a fairly well funded laboratory and demonstrates the quality of several teams (only two of them are not supported by such competitive grants).

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

The new four year term project of the LBPA will comprise 5 teams. The former team 1 will now independently develop the USR project whereas teams 2 and 7 will no longer exist. In contrast a new team (number 5 in the new project) will emerge from previous team 4.

Team 1: Dynamics of macromolecular complexes

This team headed by a DR2 CNRS includes 1 CR1 CNRS, 1 IR CNRS, 2 post-docs and 1 PhD. 1 Professor from MRC Cambridge has joined the team for a 2-year period on an ANR Chair of Excellence position. This group has developed and optimized biophysical tools (e.g. SPR) to study macromolecular interactions, which they have employed to study more particularly macromolecular assembly during control of gene expression and viral integrase binding to DNA. This team plans to develop four different projects. The first one, the regulatory dynamic analysis of eukaryotic chromatin organization at the level of reconstituted mono and polynucleosomes, is a new project relying mainly on the expertise of the visiting professor. The committee notes that funds for AFM equipment have already been obtained for this project. The second project aims to characterize the dynamic analysis of macromolecular assembly during control of gene expression in bacteria. The third project aims to conceive and develop a low-cost label-free photonic biosensor. The last project, focused on the characterization of the bacterial transcription regulatory network and its role in the maintenance of genome stability during DNA replication, will be coordinated by the CR1 scientist and may emerge as an independent group in the future.

This group has an impressive capacity to develop and optimize technologies to study macromolecular interactions. There is good interaction with the other teams of the unit due to the expertise, which is also made accessible through the Biosensor platform directed by the engineer. The level of the team's activity is very good, with publications in first-rate journals (PNAS, Nucleic Acids Res, J. Biol Chem, Nat Struct Mol Biol, Mol Microbiol), invitations for seminars, and one patent. All the planed projects are already well funded. The presence of the visiting professor (Chair of Excellence) adds significant confidence and enthusiasm for the planned experiments exploring the structure of the chromatin fiber. However the committee is concerned about the future of this group if the CR1 scientist emerges as a new independent group leader. The planed projects are too diverse for a single team, and it is not always clear what is the biological question hidden behind the development of the biophysical tools. The committee recommends that the team develops a strong project or set of projects on his own, based on a clear biological question so as to have a somewhat more focused research effort.

DYNAMICS OF MACROMOLECULAR COMPLEXES

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: Biophotonics and molecular interactions

This group is a continuation of former group 3 that was previously led by a retired (pending emeritus status) scientist. It now involves two permanent CNRS scientists (and possibly the emeritus), 1 IR CNRS, 1 Technician from ENS and two PhDs. They wish to continue a number of different projects, having in common the use of sophisticated fluorescence measurement methods: protein-DNA interactions, protein-protein interactions, quantum dots, etc.

The group very positively interacted with the integrase group (group 4 of the new project) ; this fruitful collaboration will be continued. However too many non-related projects (5-7) for a group of relatively modest size (2-3 scientists) are run in parallel. The consistency between the different projects is actually methodological, not thematic. Researchers have a good publication tract (PNAS, NanoLetters, J Biol Chem, JACS, …) but only 4 out of 17 are signed with the last author belonging to the group. The team has a highly recognized technical expertise and state of the art equipment. It has a very strong capability of raising money (1 EU project + 2 ANR-PCV + GenHomme + Biosec + 4 bilateral contracts) and develops numerous and fruitful international collaborations (China, Vietnam, Moscow).

Surprisingly for such a technically oriented activity, the group did not file any patent and is hardly involved in industrial partnerships. Even though the members of the group are strongly committed to teaching, only one PhD student was trained in the team over the last five years.

It is strongly recommended to refocus the activity of the group on a more limited number of biological topics, chosen among priorities for the LBPA.

BIOPHOTONICS AND MACROMOLECULAR INTERACTIONS

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: Structure and function of nucleic acids

The project describes three main areas of research: 1/ structural studies of HIV-1 integrase; 2/ structural studies of DNA topoisomerase II; and 3/ minus strand transfer occurring during reverse transcription of HIV-1. These different themes will be worked out by three senior CNRS researchers, 1 emeritus DR CNRS, 1 MC, 1 IE and 1 IR CNRS and 3 PhD students.

The team has an established track record in investigating DNA structure in details by NMR. The DNA labeling techniques are well-done and allow novel insights into DNA structure, in particular for the HIV-1 LTR sequences. The biophysical approaches are technically sound and involve a multidisciplinary approach using circular dichroism, fluorescence and NMR. Two of the three projects are within the overall scope of the overall research team on retroviral structures. The topoisomerase II project seems out of context with the rest of the laboratory and its chance of success might be questionable. The team should attempt to tackle a new question to replace the topoisomerase II project. Greater integration with the retrovirus team (team 4) is also suggested. In particular, the studies of the HIV-1 integrase flexible loop should provide new insight in integrase resistance.

The production of the group is fair: 20 publications over the last four years in very good specialised journals (4 Nucleic Acids Res, 4 J Mol Biol, Biochemistry, ...). In contrast to other teams of the LBPA, this one is not supported by any EU or ANR grant. The team might benefit from recruiting a young researcher with international training in protein-NMR. The equipment needs to be upgraded. Implementation of a cryoprobe and modification of electronics will be necessary to perform new heteronuclear experiments and should provide greater insights into integrase (peptide)-DNA interactions.

STRUCTURES AND INTERACTIONS OF NUCLEIC ACIDS

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 4: Functional interactions of retroviruses

The team leader that is also the head of the Unit presented an impressive array of results and projects on the biology and pharmacology of retroviral integration. The team has expanded considerably with the recent recruitment of 1 MC and 1 CR, and with the arrival of 1 MC, 1 DR (retirement in 2010) and 1 technician, due to the reorganization of LBPA, and 1 PR who has joined the unit. This team develops four projects related to the biology of retroviral elements: 1/ mechanisms and inhibition of retroviral integration, 2/ Modeling and structural bioinformatics, 3/ Foreign DNA epigenetic and 4/ Mechanisms of cell restriction to viral infection. Each project is well defined, developed by a senior/junior scientist, and well integrated with the overall goals of the team.

The scientific level of the team's activity is excellent, as judged by the publications (27 papers over the last four years: 3 J Med Chem, 3 J Biol Chem, 1 J Immunol, ...), 2 patents, numerous communications and invited lectures, national (Bordeaux) and international collaborations (Moscow, Novosibirsk) and the number of contracts (academic - ANR, ANRS- and private). The team has also developed a strong translational component with collaborations with the virology team from Pitié-Salpétrière, and with biotech companies (such as Bioalliance) for the development and licensing of original integrase inhibitors. This team also develops collaborations with the other teams of the unit.

The committee recommends that this team is given full support.

FUNCTIONAL INTERACTIONS OF RETROVIRUSES

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 5: Bacterial chromatin and gene regulation

This team, which is a spin-off of Team 1, is the smallest in size as it only involves a single permanent scientist (CR CNRS), 1 post doc and 1 PhD student. The team leader has a good publication tract (Nat Struct Mol Biol, 2 Nucleic Acids Res ...), is highly cited and obtained an independent grant from the ANR as coordinator. Recent results obtained by this group led to a paradigm shift in the way people were looking at H-NS-DNA interactions. Rather than being a non specific DNA binding protein, H-NS specifically recognizes a 10 bp long sequence motif. The leader of the team is now fully independent from her previous group (thematically and financially).

The scientist has a high technical skill. She is a recognized leader in the field. She demonstrated her capacity of getting specific funding (coordinator of an ANR-PCV 2007 grant + Blanc 2005) and to develop international bilateral collaboration with India. However this is indeed a very small group with no priority on future recruitment. If the head of the Unit wishes this team to develop and being independent, he should clearly put recruitment priorities on this group with at least one new permanent staff (technician or scientist). Presently the critical mass of the current group is questionable.

BACTERIAL CHROMATIN AND GENE REGULATION

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	B	A

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

— Management:

The head of the laboratory, who is also head of team 4, is a productive and energetic young researcher. He seems to be supported by all the members of the Unit and has the required authority/charisma. He has excellent visibility in the retrovirus community. The past two years he successfully demonstrated his ability to run the Unit in particular through the preparation of this new project. His team (n°4) plays a pivotal role in the scientific project; this should be even more prominent in the future as teams 2 and 3 might refocus part of their activity with respect to themes developed by team 4. The departure of former team 1 (oncology) does not weaken the project; it actually brings more coherence. Contacts will be maintained for shared facilities and platforms.

— Human resources:

There is a reasonable balance between researchers and technicians; the latter ones play a crucial role for platforms. The expected departure of three senior staff members is more than compensated by the recent arrival of several young researchers. Care should be taken with respect to the relative size of groups, some being pretty small.

— Scientific life:

This will be made easier now that the all Unit is located at the same place. Regular laboratory meetings are organized.

6 • Recommendations and advice

— **Strong points :**

- Overall excellent and innovative technological expertise (common to several themes : 1, 2, 5).
- The arrival of a British professor (in 2008 for 2 years) through a Chair of excellence reinforces the lab expertise on chromatin regulation and interactions.
- Excellent capacity to attract funding.
- Several recent patents.
- Involvement in teaching activities.
- Strong support from the hosting university.

— **Weak points :**

- Too many projects are developed by teams 1 and 2.
- LBPA is currently the only biology group in the campus, and this does not seem to be compensated by privileged interaction with the local physics laboratories in Cachan.

— **Recommendations :**

- Balance recruitment to compensate for size heterogeneity of the groups; provide critical mass to the smallest one (team 5).
- Attracting an ATIP/ Avenir group is an excellent goal provided this does not introduce an unrelated topic and this does not compete with the development of the recently emerged team.
- Clearly define the rules for sharing platforms/facilities/staff with the former team 1 that now runs an independent project (USR).

Laboratoire de Biotechnologie et de Pharmacologie Appliquées (LBPA)

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	A	A	A

Dr Jean-François Mouscadet
UMR 8113 – CNRS - Directeur
Laboratoire de Biotechnologie et Pharmacologie génétique Appliquée (LBPA)
Ecole Normale Supérieure de Cachan, 61 avenue du Président Wilson, 94235 Cachan cedex
Tél. : 33(0)1 47 40 76 70 - Fax : 33(0)1 47 40 76 71 ; Email : mouscadet@lbpa.ens-cachan.fr

Réponse au Comité d'experts
UMR8113

Après avoir pris connaissance du rapport d'évaluation de l'AERES concernant l'UMR 8113, la direction du laboratoire et les équipes évaluées tiennent à commenter brièvement certains des points mentionnés parmi ceux à améliorer.

Commentaires généraux

"LBPA is currently the only biology group in the campus and this does not seem to be compensated by privileged interaction with the local physics laboratories in Cachan".
Conscient du potentiel du campus de l'ENS pour un projet interdisciplinaire, le LBPA a participé activement à la création de l'IFR121 d'Alembert qui associe quatre laboratoires du campus, physique, chimie, biologie et gestion de l'énergie. La création de cet Institut s'est concrétisée par la construction récente d'un bâtiment de recherche qui réunit les moyens communs à ces quatre laboratoires. L'installation fin 2007 du LBPA dans le bâtiment de l'Institut favorise à présent une interaction renforcée entre les laboratoires notamment dans les domaines des biocapteurs et de l'imagerie moléculaire et cellulaire.

"Clearly define the rules for sharing platforms/facilities/staff with the former team 1 that now runs an independent project (USR)"
Le LBPA est actuellement opérateur d'une plateforme d'imagerie constitué d'un microscope confocal et de plusieurs dispositifs de microscopie à fluorescence résolue en temps. Cette plateforme est sous la responsabilité d'un chercheur du LBPA. L'importance prise par cette activité en particulier dans le contexte de l'IFR121 d'Alembert a conduit récemment les tutelles du laboratoire à renforcer les moyens humains mis à disposition du LBPA pour ouvrir plus largement cette plateforme. En parallèle, le nouveau projet d'USR LOMP prévoit également le développement d'une plateforme d'imagerie cellulaire adaptée à ses activités. Dans ce contexte, les deux laboratoires ont décidé de mettre en commun leurs moyens pour développer une plateforme commune dans l'intérêt des chercheurs des deux unités et plus largement de l'ensemble du site de l'ENS Cachan. Les règles d'utilisation et de maintenance des appareils seront déterminées par une convention liant les deux unités, sous l'égide de leurs tutelles.

Commentaires spécifiques sur des équipes

D'un point de vue global, le nombre et la nature des thématiques considérées pour le projet de renouvellement du laboratoire ont fait l'objet d'une réflexion approfondie des chefs d'équipes et de la direction d'unité. Toutefois le comité d'évaluation pointe encore le danger d'un nombre jugé encore excessif de projets. De ce point de vue, plusieurs équipes ont souhaité apporter les commentaires suivants dans le but d'expliciter leur démarche.

Equipe 1"The planed projects are too diverse for a single team "
Les projets présentés par cette équipe nous paraissent liés par deux caractéristiques originales. Premièrement, une question biologique centrale, à savoir comment la régulation génique est reliée à la structure de l'ADN et à sa condensation, qui implique clairement des mécanismes et des principes communs aux eucaryotes et aux procaryotes. Deuxièmement, des méthodologies en place ou développées par l'équipe pour étudier cette question fondamentale qui nécessitent des développements technologiques aux interfaces capables de mesurer dynamiquement les changements conformationnels associés à la formation d'assemblage macromoléculaires. L'équipe souhaite donc réaffirmer sa conviction de posséder une combinaison originale de pré-requis théoriques et pratiques pour aborder avec succès cette thématique. Le développement du quatrième projet par le CR1 issu de l'équipe est une extension logique de l'expérience acquise dans le groupe et de son désir d'étendre celle-ci dans une direction originale sans affaiblir aucunement la thématique principale du groupe.

Equipe 2 « *too many non-related projects* »
Les préoccupations de l'équipe 2 sont d'ordre thématique. Cette équipe s'intéresse à la compréhension des mécanismes de reconnaissance entre biomolécules, essentiellement protéine-ADN et protéine-protéine. S'il est indéniable que plusieurs systèmes sont étudiés par des méthodes d'investigations basées essentiellement sur l'utilisation de la fluorescence, l'équipe n'a pas vocation première à faire du développement instrumental. L'absence de brevet lié au développement technique comme la nature des travaux de l'équipe publiés pour la majorité dans des journaux à vocation généraliste relève de cette orientation. Ceci étant, tant le nouveau responsable l'équipe 2 que la direction de l'unité seront très attentifs à la cohérence et à la bonne conduite des projets concernant les ressources financières et humaines affectées. Concernant cet aspect et, comme il a été justement souligné, la plupart des projets sont d'ores et déjà financés.

*Equipe 3: "The topoisomerase II project seems out of context with the rest of the laboratory and its chance of success might be questionable***"**
Les études concernant la Topoisomerase ont été récemment réorientées dans une direction susceptible de fournir des résultats originaux dans un contexte international compétitif, en valorisant l'expertise technique originale de l'équipe concernant les acides nucléiques et

notamment une nouvelle technique de marquage d'ADN mise au point pour étudier la dynamique particulière de séquences caractéristiques. Cette réorientation a d'ores et déjà été à l'origine d'une production assez importante (1 J.Mol. Biol.2008, 1 J. Phys.Chem B, 2007). L'objectif du recentrage de ce thème vers l'étude des structures d'ADN reconnues par cette enzyme est bien de renforcer une expertise spécifique qui pourra être appliquée à terme à d'autres modèles.

Equipe 5: "Presently the critical mass of the current group is questionable".
La direction de l'unité a conscience que la pertinence d'une équipe de taille très limitée demeure sujette à discussion. Néanmoins, son caractère d'indépendance tant financière que thématique nous a paru justifier pleinement de sa création. En accord avec la reconnaissance par le comité d'évaluation du niveau scientifique du projet, son renforcement en moyens humains sera une priorité du prochain quadriennal.

Cachan, le 26 mars 2009

Jean-François Mouscadet
Directeur de l'UMR8113