Laboratoire de génétique et de biologie cellulaire

Rapport Hcéres

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

Section des Unités de recherche

Evaluation report

Research unit :

LGBC (Laboratoire de Génétique et Biologie Cellulaire)

UMR 8159

University : Saint-Quentin-en Yvelines

March 2009

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et de l'enseignement supérieur

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LGBC (Laboratoire de Génétique

et Biologie Cellulaire) UMR 8159

University : Saint-Quentin-en Yvelines

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 : LGBC (Laboratoire de Génétique et Biologie Cellulaire)

Requested label : UMR CNRS

N° in case of renewal : UMR 8159

Head of the research unit : M. Bernard MIGNOTTE

University or school :

Saint-Quentin-en Yvelines

Other institutions and research organization:

CNRS

EPHE

Date(s) of the visit :

January 27th 2009

Members of the visiting committee

Chairman of the commitee :

Ms. Anne-Odile HUEBER, University of Nice-Sophia Antipolis, France

Other committee members :

M. David DURANTEL, University of Lyon 1, France

Ms. Urszula HIBNER, University of Montpellier 1and 2, France

M. Ted HUPP, University of Edinburgh, UK

M. Hermann STELLER, The Rockefeller University NYC, USA

M. Peter VANDENABEELE, University of Ghent, Belgium

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

CNU Ms. Chantal ASTIER, Gif sur Yvette, France

CNRS M. Michel RIGOULET, Bordeaux, France

Observers

AERES scientific representative:

M. Philippe BOUVET

University or school representative:

M. Jean Francois JEANNIN, EPHE : Ecole Pratique des Hautes Etudes

M. Gérard CAUDAL University Saint Quentin en Yvelines

Research organization representative (s) :

Mrs Evelyne JOUVIN-MACHE CNRS (excusée)

Evaluation report

1• Short presentation of the research uni

The unit includes 47 members as follows:

- 20 researchers with teaching duties
- 3 full time researchers
- 9 engineers, technicians and administrative assistants
- 2 post-doctoral fellows
- 13 graduate students, all funded
- Number of HDR : 7
- Number of PhD students who have obtained their PhD since January 2005 : 9
- Numbers of "publishing" researchers with or without teaching duties : 22 out of 23

2 • Preparation and execution of the visit

The visit was prepared through emails and phone call exchanges between the AERES representative and the Evaluation Committee director, taking into account directives transmitted by the AERES. The committee members received a written report which provided a short description of the activities and projects of all groups prepared by the director of the unit and Email communication between the different committee members was used to prepare the on-site evaluation process.

A brief overview of the visit schedule and some specific comments of the visit process are given below.

8h30 to 9h: Door-closed meeting with the Committee members and AERES representative

9h to 9h45: Presentation by the head of the lab: past activity and projects

9h45 to 10h30: Presentation by the team "Mitochondrial protein complexes and apoptosis ".

10h30 to 11h15: Presentation by the team "Stress and cell death".

11h15 to 12h00: Presentation by the team "Cell memory and signalling".

12h00 to 12h45: Presentation by the team "Molecular Virology".

12h45 to 14h30: Lunch and poster presentation by team members

14h30 to 15h00: Meeting with PhD students and postdoctoral fellows

14h30 to 15h00: Meeting with engineers, technicians and administrative assistants/researchers/PhD-Post docs

15h00 to 15h30: Door-closed meeting: Committee members, AERES representative, University and Research Organization representatives (University de Versailles St Quentin, Ecole Pratique des Hautes Etudes, CNRS)

15h30 to 17h30: Committee deliberation: Door-closed meeting with the Committee members, and AERES representative

The experts had a first closed-door session (30 min) to prepare the review and to listen to the representative of the AERES explaining the AERES policy. The general presentation by the director was clear and allowed to clear out of some specific general organisation points for the unit that were not complete enough in the written report (especially the future plans and move of the institute). Individual presentations by the group leaders summarized their activities and their plans for the future, in the presence of all members of the team. All talks were followed by questions from the visiting committee. Lunch was informal, allowing exchanges with the group leaders, the director and the scientific staff. Just after the lunch time, a short but informative poster session (9 in total) allowed committee members to deepen scientific questions to learn more about some specific projects or orientations and to meet the personnel. In the afternoon, the committee separated in three subgroups in order to meet individually with students/post-docs, scientists with permanent position and technical staff. Lastly, the committee met privately to discuss the review. During this private session, the Committee received the director for a short discussion.

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

This Unit includes 4 teams and presents a sociable and "familial" working atmosphere. Its main research themes are cell death processes and virus/hosts interactions. As the only biological research unit on the university campus, the unit appears scientifically isolated. However, close and long lasting academic exchanges and collaborations with national and international research institutions exist and at least in part compensate for the physical isolation. The 4 teams are in fact independent groups, with a good support provided by the laboratory director. A weak aspect is that the teams are involved in too diverse fields and that the laboratory suffers from lack of a clear scientific strategy. Indeed, it is not very clear what is the mutual added value of the 4 research programs, since the aims and actions they share were not clearly identified during the visit.

54 peer-reviewed articles have been produced since 2005. During the same period 7 PhD students have successfully defended their theses and 13 PhD are currently in progress.

The Unit hasn't invested important resources in dedicated equipment (except for a flow cytometer recently), additional technology platforms and core facilities are available on-site and on neighbouring campuses.

Of further note is the considerable number of staff members strongly involved in university teaching and others tasks. A positive aspect is that this allows them to attract motivated young PhD students, as witnessed by the flow of PhDs, all members participating in their supervision. A weak point is the very heavy teaching load that might slow down the scientific productivity of the teams.

The commitee noticed a clear structural underfinancing and wishes to express the need for engagement within european networks and additionnal interactions that would help push forward their scientific productivity.

The committee feels that a better evaluation process would have been facilitated by a more detailed and better prepared written report. This has been particularly harmful for the presentation of the future project (creation of a new research structure in the faculty of medicine in Montigny-le-Bretonneux (Saint-Quentin-en Yvelines)).

The installation of the unit within the new structure is planned at the beginning of 2011. It is presented as an unique opportunity to develop new partnerships and to open access to technological platforms essential to their research activities. The main objective is to constitute in the next decade a biomedical pole of research on the topic of Environment and Cellular Physiopathology, which will include about 250 researchers and teacher-researchers in relation to the "Groupement d'Intérêt Scientifique" Climate-Environment-Society. However, in the absence of more detailed informations concerning the setting of this new research unit, the committee could not undertake an in depth analysis of the future unit project and therefore make recommendations about this strategic choice. These comments were made during the visit and it was clear that the director was aware of the problem and concerned by this point. The representatives of the University and of the regional CNRS administration expressed a strong support both of the present unit and of the future projects. Nevertheless, the fact that the project was not previously discussed with the CNRS at a national level was found rather surprising by the committee. Again, an exchange with the director about this specific point made it clear that he was aware of the importance of this lack of communication, a point which he will make an effort to improve.

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

Team : Mitochondrial Protein Complexes and Apoptosis

This team, composed of 1 full time researcher, 4 researchers with teaching duties (3 assistant professors (MCF) and 1 professor), 4 PhD students, 1 post-doc and 1 technician, works on an interesting and important problem in cell death research, namely the role of mitochondria during apoptosis. Previous efforts have largely focused on the adenine nucleotide translocator (ANT) and its role in mitochondrial membrane permeabilisation (MMP). The lab head initiated this work as a postdoc within a CNRS unit in Villejuif, and the current project is a continuation of these earlier studies. A pro-apoptotic role of ANT has been proposed as early as 2000, but considerable controversy remains whether ANT plays any direct role in apoptosis. Work from this team during the past project period has revealed considerable complexity due to the presence of at least four different isoforms of ANT, and it remains to be determined which, if any, of these isoforms play a physiological role in the regulation of cell death. The PI of this group also works on lethal inter-organelle communication, resistance mechanisms of lung cells to chemotherapy, and deregulation of apoptosis in fatty liver. These projects are original and were initiated during the previous funding cycle. As a result, they are still in their infancy and have not yet made an impact on the field. Overall, this team conducts a rather large and diverse set of projects that are all interesting, but it will be important to set clear priorities and develop a more focused and detailed research plan. On the positive side, the team's productivity has been good and the research offers potential translational opportunities since many findings in this field are relevant for the treatment of human diseases. Furthermore, an inhibitor of ANT has been identified and additional small molecules may be developed in the future. However, enthusiasm for this project is somewhat dampened because the project is over-ambitious and the work is not sufficiently focused. For example, critical information regarding the properties of ANT inhibitors was not presented, and the proposal does not include a rigorous path to test the physiological function of the different ANT proteins. This is and important issue, since genetic studies in mice have failed to reveal a pro-apoptotic role of ANT, and 9 years after the initial proposal that ANT promotes apoptosis this hypothesis remains tenuous. Given the early stage and wide range of the various other research aims, the team would benefit from developing a rigorous and more focused research plan.

MITOCHONDRIAL PROTEIN COMPLEXES AND APOPTOSIS

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	A	B	A	B

Team : Stress and cell deaths

This team is composed of 2 full time researcher, 9 researchers with teaching duties (7 assistant professor (MCF) and 2 professors), 5 PhD students, 1 post-doc and 3,5 technical staff. Although led by the director of the department, it is in fact composed of three small, semi-independent groups, each with an individual scientific history and project, there are sufficient common interests and experimental approaches to give coherence to the team's common project. Historically, the team was involved in the initial identification of the mitochondrial membrane potential changes as a key event of apoptosis. They continue to tackle major questions in the field of apoptosis. Intelligent use of Drosophila genetics to validate original findings made in less sophisticated cell culture models is a strong point in the activity of this team. The previous discovery of novel ubiquitin-degradation pathways that control Bax turnover should also be noted, as the ubiquitin proteasome system is an up and coming high priority drug discovery area for pharmaceutical companies. Their apparent commitment to use proteomics to discover the interactome for p53 in the mitochondria, and to tackle a difficult question of protein aggregates in degenerative disorders are also interesting. In isolation, each of these projects is quite novel, thoughtful, and could form a continuing research programme if successful. However, while some of the findings are interesting and intelligently exploited, their research interests concern highly competitive fields of the role of p53 and Rb tumor suppressors and of the cell death inducing mechanisms of protein aggregation. Despite the intense international competitiveness in this area, it is commendable that the team has identified novel regulation of Rb by proteolysis. In addition, identification of the mitochondrial partner of p53 has not been solved by any means and this team might have the potential to significantly contribute in this area if they are successful and choose to focus on this problem. It would certainly be worthwhile to better define the questions that can be usefully asked by this small team. In summary, while the team needs to stay in a mainstream of apoptosis research to secure funding, the committee suggests improving their focus and defining a limited number of specific and original themes that they will address in the future. This is especially true for the work on mammalian cell lines. Indeed, the field of studies is very competitive and, although the group has the potential to produce significant results their current lack of focus may not lend itself to solving any of these problems.

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Team : Molecular Virology

This team is composed of 3 researchers with teaching duties (2 assistant professor (MCF) and 1 professor), 2 PhD students, 1 post-doc and 1,5 technical staff members. The PI is interested in the characterisation of molecular mechanisms involved in the viral persistence of Hepatitis B virus. This group has focused on P22 protein, which is initially targeted to ER and is the precursor of the HBe antigen (HBeAg). They demonstrated that P22-cyt and P22-ER sequences are identical. Dominant negative mutants were used to confirm that the P22 has hijacked the ER associated degradation pathway (ERAD). They evidenced that P22 escapes from proteasome degradation because a low lysine content which allows an ineffective polyubiquitinylation. A specific interaction between P22 and Grp78/Bip, an ER-chaperon protein, was also demonstrated, which could explain the Grp78/Bip relocalisation to the cytoplasm and the subsequent activation of the unfolded protein response (UPR). They have characterised the amino acids involved in the P22/gC1qP interaction and the role of this complex in apoptosis was studied to some extend. Eventually, immune cell partners of P20 and HBe and functional effects of HBV proteins on immune cells were searched and interesting preliminary data, yet unpublished, were obtained. In the future, i) the consequences of P22 retro-transport to cytoplasm on the viral cycle and the viral persistence will be further investigated at a molecular level and ii) the functional effect of P20 and HBe viral proteins on immune system will be developed. This work will help elucidate the role of precore protein in viral persistence and also should shed light on common escape strategies developed by other viruses responsible for persistent infections as HCV and herpes. The team has published moderately in respected international journals (JBC, Gene..) and has obtained some funding from ANRS. It is however clear that additional funding would have benefited its research activity and publication record. It is noteworthy that this group suffered from over-teaching activities, which could partially explain its moderate scientific production. However, the PI, over the years, managed to establish himself as a fairly respected actor in the HBV field, which should be beneficial to perpetuate this group. The PI will retire early in the next contact. Two young scientists, both MCU, will develop the two main aforementioned projects.

MOLECULAR VIROLOGY

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

Team : Apoptosis and development

This team is composed of 4 researchers with teaching duties (3 MCF and 1 PR), 2 PhD students, and 1 technician.The PI has been working on cell death processes in the context of development and viral infection, using the *Drosophila* system. His group studies how cell death plays a role in morphogenesis and cell counting in organs, more precisely in controlling the numbers of retinal pigment cells and number of ovarioles in developing ovarium. The group continued the work on chromatin binding epigenetic factors (BAN, TRL, PSQ) that regulates the Hox gene expression (Faucheux et al. MCB 2003). The group realizes the high competition in the field, and therefore defines her niche on the role of DRONC/DRICE caspases and BTB/POZ nuclear factor in cell counting in the ovary, and on the molecular and functional characterization of the chromatin complexes involving BAN, TRL and PSQ,

The overall scientific production of this group the last four years has been low with only one research article (Int. J. Dev. Biol. 2008). This low output is quite amazing since the PI gave a convincing and well-structured oral presentation on his past and future work. The committee is convinced that this group has a much larger potential than the actual output. The research of this group is very well focused on a precise biological questions and limited to a set of molecular targets. The methodologies and approaches are adequate, systematically and logically sound. The data presented are of high technical quality and contain the required controls. This should be a strong basis for more scientific output. We would like to recommend the PI to continue his focused and hypothesis-driven approach, but to aim at higher impact publications. He has proven to produce interesting and well-controlled data, but does not come to publishing them. He may also aim at integrating functional genomics with dissecting molecular mechanisms using mass spectrometry in collaboration with expert groups. This should allow him to create more interactions (and funding opportunities) at national and international level in a unique expert domain (cell counting in ovaria). It can be hoped that the new recruited faculty member will enforce this focus. In conclusion, the committee encourages the PI to aim higher international visibility; the quality of his work deserves it.

APOPTOSIS AND DEVELOPMENT

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
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5 • Appreciation of resources and of the life of the research unit

- Appreciation on the quality of the management:

Despite the fact that the general organization (respective roles of the director and the group leaders in the general running of the unit, policy of budget repartition, composition and period meeting of the Laboratory Council …etc) of the institute was not clearly described either in the written report nor in the oral presentations, the on site visit allowed to notice a clear management strategy.

- Appreciation on the human resources:

Discussions with representatives of the different staff categories have been direct, positive and really helpful for the committee's members. Overall, the committee got the impression that technicians, students and permanent researchers were generally pleased by the familial working atmosphere within the unit. In addition, the mean duration of a PhD is in the norm for this research field (average: 3,5 years) and apparently all PhDs found employment in public organizations or private companies.

- Appreciation on the communication strategy:

In addition to the weekly lab meetings, several regular events are organized to favour scientific exchange: (1) monthly seminar of an invited speaker (external scientists), (2) bi-weekly meeting dedicated for members of the lab who are using drosophila as a model system; (3) every four months, scientific meeting of all members of the lab where each group presents in turn its results and its projects. Two International Symposia on "Apoptosis and mitochondria: from normal to pathological signalling in viral infection and cancer" were organized by the unit during the last quadrennial;

6 • Recommendations and advice

- Strong points

Very good potential for original and important contributions.

Nice sociable working context. Students are happy about integration of education and research, good contacts between staff and students, solidarity between research groups in exchanging techniques and scientific discussions: in conclusion very supportive atmosphere for students and technical staff.

Strong commitment to teaching.

- Weak points:

Too high proportion of researchers with a very heavy teaching load.

Insufficient funding and scientific publications.

The unit is quite isolated on the campus, lacking of major technological platforms and integration in national and international programs. This is certainly one of the reasons for lack of attractively towards post-docs and full time researchers.

No structured plan yet for the move to the new campus. What will be the possibilities for integration with existing research groups? What will be the nature of technical platforms (advanced imaging, mass spectrometry, transgenic facility, etc.).

Continuation of Molecular Virology group is unclear (retirement of the PI in one year) and has not been addressed.

- Recommendations

This is a small, rather isolated and poorly funded unit. It is in fact quite remarkable that their scientific production is rather good, illustrating their capacity for innovative work. We believe this unit deserves the credit for what they have achieved under relatively difficult working conditions.

The proposed move to a new location might improve the critical issue of isolation and poor access to technological platforms; it is most unfortunate that very little information on this project was presented to the committee.

An effort is needed to engage in collaborations likely to improve the projects' funding and increase its attractivity for young researchers and post docs.

Diversity of the department should be counteracted by increased interconnectivity between research programs (common research goals, common research tools, collaboration)

Increase globally the level of publication. In addition, a better implementation of technology platform might help to reach for higher impact papers.

A PhD thesis committee should be installed. Increase support for participation in international meetings.

Laboratoire de Génétique et de Biologie Cellulaire

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

LABORATOIRE DE GENETIQUE ET BIOLOGIE CELLULAIRE
UMR 8159 UVSQ/EPHE/CNRS

Université de Versailles Saint-Quentin-en-Yvelines,
45 avenue des États-Unis
78035 Versailles cedex

Bernard MIGNOTTE
Professeur à l'UVSQ
Directeur

Comité d'évaluation de l'AERES

Objet : Réponse au rapport sur le LGBC (UMR8159)

Versailles le 20 mars 2009

Cher(e)s Collègues,

Nous vous remercions pour l'évaluation très détaillée de notre unité. Nous sommes sensibles aux compliments que vous nous avez faits, mais aussi à vos remarques et recommandations dont nous avions déjà pris note lors de votre visite du 27 janvier 2009.

Remarques générales

Nous souhaitons tout d'abord apporter quelques précisions sur le projet de déménagement de l'unité à Montigny-le-Bretonneux (St Quentin-en-Yvelines), à propos duquel nous avons par ailleurs demandé un rendez-vous avec la direction de l'Institut des Sciences Biologiques du CNRS pour présenter le projet de manière plus détaillée que ce que nous avons déjà fait par le passé, car nous tenons fortement à maintenir un partenariat fort avec cet organisme.

Ce projet est partie intégrante d'une demande actée au CPER (Ile de France) dont l'objectif est d'installer une structure de recherche au sein de l'UFR de médecine. L'enjeu pour l'Université est de constituer dans la prochaine décennie un pôle de recherche biomédical qui comprendra de l'ordre de 250 chercheurs et enseignants-chercheurs. Ce campus, qui sera le plus grand campus universitaire de l'ouest de la région parisienne, offrira notamment de nombreuses plateformes technologiques. Ce projet se situe dans le cadre d'un partenariat public privé (PPP). L'université a obtenu l'accord du ministère des finances et nous en sommes actuellement au stade du dialogue compétitif. Le partenaire privé sera choisi en août 2009 et l'objectif est d'installer les laboratoires dans ce nouveau bâtiment fin 2011.

La recherche y sera organisée en deux pôles : un pôle "Epidémiologie" et un pôle "Biologie". C'est dans le cadre de ce deuxième pôle que nous voyons notre intégration. Pour ce qui concerne les laboratoires existants de l'UVSQ, le pôle "Biologie" comportera, outre notre unité, l'EA 3647 "Laboratoire physiopathologie et diagnostic des infections microbiennes", l'EA 4339 "Laboratoire Peau, environnement, cancer", l'EA 4340 "Epidémiologie et oncogenèse des tumeurs digestives", l'EA 4342 "Laboratoire d'étude de la réponse neuroendocrine au sepsis" et une EA en demande de création : "Complications uro-génito-sexuelles du handicap neurologique et moteur". Certaines de ces équipes développent déjà des projets en collaboration avec des équipes du LGBC. D'autres responsables d'équipe - chercheurs dans un EPST - couvrant des thématiques proches des nôtres (mort cellulaire et interaction hôte/agent infectieux) ont aussi manifesté leur intérêt pour nous rejoindre. Un appel d'offre officiel sera lancé dès que possible.

D'un point de vue pratique, nous disposerons dans ce nouveau cadre de plates-formes (Microscopie électronique, Microscopie confocale, Transcriptome, Protéomique,

Animalerie). Ces équipements seront financés en partie par l'UVSQ mais nous répondrons aussi aux différents appels d'offre des associations caritatives et des collectivités locales dont la région Ile-de-France (DIM "Santé - Environnement – toxicologie", appel à proposition Sesame…). L'accès à ces plateformes, dont le comité de visite a souligné l'importance, nous sera donc facilité dans ce nouveau contexte.

Remarques concernant spécifiquement les équipes

L'équipe "Mitochondrial protein complexes and apoptosis" souhaite préciser que les informations concernant les inhibiteurs d'ANT sont confidentielles en raison de la collaboration sur ce thème avec la société pharmaceutique Theraptosis et en l'attente d'un dépôt de brevet en France et en Europe, le brevet USA étant déposé (recommandation du service de valorisation de la recherche de l'UVSQ).

Les activités des 3 groupes qui constituent l'équipe "Stress and cell death" ont déjà été resserrées. En particulier, le groupe travaillant sur les cellules de mammifères se consacre désormais à l'étude de l'interaction p53/mitochondries dans les cellules vivantes et au rôle de la caspase-9, sous ses différentes formes, dans l'activation de la voie mitochondriale de l'apoptose induite par p53. Les autres thèmes abordés par ce groupe (concernant la protéine pRb) ont été arrêtés entre la rédaction du document écrit et la visite du comité, et les données obtenues vont être publiées. Les 2 autres groupes développent des projets communs sur le processus de compensation chez la drosophile.

La recherche d'un successeur à la tête du groupe "Molecular Virology" est entamée (avec un DR-CNRS et un DR-INSERM). La perspective de l'installation à Montigny nous permet d'envisager plusieurs possibilités.

Des comités de thèse seront mis en place dès la rentrée 2009 dans la cadre de la politique de l'Ecole Doctorale GAO à laquelle nous sommes rattachés.

Nous vous remercions de votre travail d'expertise et vous prions de croire à nos sentiments le plus cordiaux.

Bernard Mignotte

Tél. : (33) 1 39 25 36 50 - Fax : (33) 1 39 25 36 55 - Courriel : bernard.mignotte@uvsq.fr