Génétique fonctionnelle de la prolifération et de la différentiation cellulaire

Rapport Hcéres

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

Section des Unités de recherche

Evaluation report

Research unit :

Functional genomics of normal and cancer cell proliferation and differentiation

University Paris11

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Evaluation report

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University Paris11

Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

November 2008

Evaluation report

The research unit:

Name of the research unit: Functional genomics of normal and cancer cell proliferation and differentiation

Requested label: UMR CNRS

N° in case of renewal: FRE 2944

Head of the research unit: Ms. Annick Harel-Bellan

University or school :

University Paris 11

Other institutions and research organization:

CNRS

Date(s) de la visite :

November 28th, 2008

Members of the visiting committee

Chairman of the commitee:

M. Robert FEIL, (University of Montpellier), France

Experts :

Ms Andrea MUNSTERBERG, (University of Biological Sciences) , Norwich, UK

M. Niall DILLON, (University of London), UK

M. Anders LUND, (University of Copenhagen), Danemark

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

M. Thierry GRANGE, Paris, CoNRS representative

Observers

AERES scientific representative:

M. Philippe Bouvet, Lyon, France

University or school representative:

M. Dominique Emilie, University Paris 11

Research organization representative (s)

Ms. Urszula HIBNER, CNRS

Ms. Martine DEFAIS, CNRS

Evaluation report

1 • Short presentation of the research unit

- Numbers of lab members including researchers with teaching duties, full time researchers: 7
- Engineers, technicians and administrative assistants: 5
- Numbers of HDR: 3
- Numbers of PhD students who have obtained their PhD: 6
- Average length of a PhD during the past 4 years; 4 years
- Numbers of PhD students currently present in the research unit: 5
- Numbers of PhD students with fellowships: 5
- Numbers of lab members who have been granted a PEDR: 0
- Numbers of "publishing" lab members: 7

2 • Preparation and execution of the visit

The preparation of the visit by the Director and the different groups of the new unit was good, also as concerns the provided written documentation, which was updated for the day of the visit. This allowed the Committee to have the required information at hand and to work efficiently through the day's programme. The committee gave special consideration to the fact that this unit goes through a period of transition, with several groups having left the institute recently, and others that are starting and are bringing new themes into the unit. The evalution therefore considered the unit's future potential besides the group leaders/teams' past achievement. Complementarity and future interactions between the four groups of the unit were also among the discussion points on the agenda. In addition, together with the representatives of the research organisations and the University Paris 11, the Committee considered the infrastructure of the unit, particularly in the context of the André Lwoff Institute and the research campus. This part of the day's programme aimed at discussing how aspects could be enhanced such as to help the groups to produce independent high-quality science, but also to facilitate the possible recruitment of additional group leaders in the future.

The day's programme was structured as follows:

First closed-door Committee meeting to discuss the aims (AERES) and the organisation of the visit.

General presentation of the unit by the Director: Scientific policy, infrastructure, financing and administration, future plans.

Presentations (40 minutes/group, followed by some 15 minutes of questions) by the group leaders explaining their projects and how these fit into the unit.

A Poster Session during lunch time with posters from all the groups. This was very much appreciated by the committee members and allowed them to interact informally with students, researchers and the technical personnel.

Short meetings with PhD students, postdoctoral researchers, technical personnel administrative staff, and permanent researchers (non-group leaders), respectively.

Meeting of the comittee together with the observers of the CNRS and University of Paris-Sud XI to discuss about the unit and the research campus.

A closed-door meeting of the Committee to evaluate the research groups and the unit. This concluded the visit of the unit.

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

During the last few years, this research unit developed diverse projects which overall have led to a scientific output of high quality. The main theme of the laboratory had been on 'epigenetics and cancer'. However, because of the move of four of its group leaders to other institutes in France (see below), and the recent recruitment of two new group leaders, the themes of research have changed in part. Whereas the accent will be less on chromatin regulation during development and on prolifrating/differentiating cells in the future, a greater emphasis will be given to the function and mode of action of micro RNAs (miRNAs) and other small non-coding RNAs. Already, the unit had been studying in detail for some non-coding small RNAs their involvement in proliferation and differentiation in normal and cancer cells. Through the establishment of the new groups, several new research lines related to the processing and recognition will be developed. These new themes concern the regulation and function of RNA binding proteins, and the exploration of a translational regulator (CPEB) and its interaction with miRNAs. Despite its relatively small size, this research unit presents a coherent and interactive research programme with a major emphasis on the developmental regulation of (small) RNAs, their recognition by specific proteins, and the various effects on translation. The programme uses different cell-based models, including muscle differentiation, and animal models. In addition, the programme includes studies on human cancer. The committee is favourable of this change in emphasis of the unit and it views positively the combination of research themes that are presented for the coming years.

Not included in the future plans are four former groups of the unit, which were all headed by researchers who took up postions elsewhere in France during the last years. In the case of two of these groups, some members opted to stay and have now integrated into the current four groups of the unit. Briefly, one of the former groups developed research to explore chromatin architecture and repressive chromatin modifications at E2F target genes in differentiating cells, with a particular emphasis on diferentiating muscle cells. This junior group moved to a novel institute in Paris and is interested in persuing this chromatin-based reseach line. Another group with complementary interests has explored histone variants, nucleosomes and chromatin assembly, giving rise to several high-quality papers. This group leader moved to the IGBMC in Strasbourg. A third group which was discontinued at the unit, performed more structurally oriented research, also in relation to protein ubiquitination of target proteins and variant histone H2AZ deposition. Finally, the fourth group which left the unit performed research on interfereon induced antiviral restriction activities in mammalian cells. It also developed an interest in exploring therapeutic agents for lymphoproliferative and auto-immune syndromes. During the last four years, the four departed groups produced interesting science with a good to excellent publication output per group leaders. These four former groups are not part of the specific evaluations provided by the committee below (paragraph 4).

In addition to its more basic approaches, the unit has been exploring in a strategic manner the possibility of using siRNAs as therapeutic tools. This is being done in mouse models, with a particular emphasis on cancer. Importantly, the unit has also developed an efficient and interactive Platform for high-throughput RNA interference (called PARi). This platform is dedicated to the high-throughput transfections in microtitre plates and to cell-based functional assays. It acquired a commercial genome-wide siRNA library comprising 23000 human genes with about 4 siRNAs per gene. This Platform is open to collaborations with external groups, and several of these have been initiated during the last few years in relation to infectious diseases, cancer and chromatin modifications.

The unit is housed in the André Lwoff Institute, which is part of the IFR89 at the Villejuif Campus. It is affiliated with the CNRS and the University of Paris 11 and has contacts, at different levels, with close-by other institutes. Clearly, this unit is one of the strong elements of the campus and the IFR, with good future potential and an excellent national and international visibility. For instance, the committee noted that the unit and its Director are involved in several French and European collaborative programmes, and these concern the different main themes of the groups.

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

Team 1 :

The group has made considerable past contributions on fundamental aspects of the biology of prostate cancer. This work was focused particularly on the anti-angiogenic effects of thrombospondin 1 (TSP1) on prostate tumours and the ability of the tumours to acquire resistance to this effect. During the period currently under review, these observations were extended to the study of the role of vascular endothelial growth factor (VEGF) in permitting tumour escape from the effects of TSP1 and the regulation of the VEGF1 gene. The group has also become increasingly focused on developing RNAi-based strategies for treating prostate cancer by knocking down VEGF. A chaperone complex that interacts with the androgen receptor was also identified as a potential target for RNAi. A startup company has been formed to pursue RNAi-based approaches for treating prostate cancer. The RNAi approach to cancer therapy faces strong competition from large international groups and pharmaceutical companies. To maintain their position in the longer term, a small group such as this will need to go beyond simply testing different siRNA molecules and address in more depth the problems that affect strategies for obtaining effective delivery of siRNA to prostate tumours in vivo. Parts of the future strategy that was presented do fit with this goal and it is suggested that this should become a major focus for the future research of the group.

A major challenge faced by any group pursuing this type of strategy for prostate cancer is the identification of an appropriate animal model for testing RNAi approaches. The current approach used by this group involves the use of prostate tumours that have been xenografted into mice. Past experience suggests that this strategy has limited long-term value for testing approaches that can be translated into a clinical setting. This could be addressed by exploring the use of transgenic mouse models for prostate cancer, which have the potential to provide a more physiological model for the disease. A restriction on this avenue of research is posed by the limited animal facilities that are currently available to the group on site. Unfortunately, the presence of the National Transgenic Facility seems to be actually restricting the availability of good animal facilities to the groups on the Villejuif site because most of the resources for animal work go into the Transgenic Facility. This is a problem that will need to be addressed if serious in vivo cancer biology research is to be pursued on the site.

Nom de l'équipe : Contrôle de l'angiogénèse et de la proliferation tumorale

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	A	B

Team 2:

This team is headed by the Director of the unit and has a first-rate publication record over the last 4 years, with papers that were accepted in high impact journals including two in Genes and Development, one in Nature Cell Biology, one in Oncogene, and three in EMBO journal and EMBO reports. Just prior to the beginning of the assessment period, the laboratory has changed its research focus from transcriptional regulation during cell differentiation to post-transcriptional regulation. Here the focus is on microRNAs in cellular models of muscle differentiation. In this area the lab has begun to make significant contributions and the lab head is frequently invited to speak at international conferences. The lab head has secured external funding in this area and is a member of different FP6 EU network programmes illustrating their achievements .

The group leader attracted talented young researchers and PhD students who are enthusiastic about their projects and the working atmosphere and environment of the lab. The students have the opportunity to present their research within the unit and also at national and occasionally international conferences.

They currently plan to set up a student association to foster scientific discussions and exchange as well as social interactions. The researchers and research project of the group are well supported by technical staff and a secretary.

In addition, an RNAi screening platform was established under the guidance of the current laboratory head.This platform has been supported by two technical staff who were recently joined by a researcher with Bioinformatics expertise. The RNAi screening platform appears to produce good outputs as a service to this and other laboratories. The data sets produced form the basis for many of the current, cutting edge projects of the laboratory. The longer-term survival of this platform will depend on the continued effective use by interested parties and this will need careful planning.

The group leader has fostered the career development of an outstanding Senior Postdoctoral researcher, who will shortly move out of the lab but stay within the unit to set up an independent group (team 3). Another recent initiative is the establishment of a communications officer, who will facilitate knowledge dissemination to the scientific community and to the interested public. Overall this is a successful team with a dedicated leader.

Nom de l'équipe : Regulation post-transcriptionnelle de la myogenèse

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+

Team 3:

This is a new junior group formed by a member of the group of the unit leader. The new team leader is young and dynamic and has played a central role in the scientific production of her former team. The proposed research programme addresses the functions of specific RNA binding proteins in the balance between proliferation and differentiation of skeletal myoblasts. Amongst the proteins of interest are Lin28 and the Lin28 associated 'IGF2 mRNA binding proteins' (IMP), and in particular IMP2 on which detailed studies will be undertaken to assess its role in mRNA translation.

The team leader has the potential to become a successful group leader. She has convincingly demonstrated her scientific capabilities and the team is expected to be successful. External development should be encouraged in the coming years, and, meanwhile, the production of independent research papers that are necessary to establish externally the credibility of this new team. Although the committee strongly encourages this group leader, it feels that internal promotion is not necessarily the best way to develop an independent research line (see below).

Nom de l'équipe : Petits arns et contrôle de la prolifération/différérenciation

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 4:

This is a newly established group planned to start in March 2009. As such, the committee is unable to review the past performance of the group. The new group focuses on translational control mechanisms involving the translational regulator CPEB. The group leader has a long standing interest in translational regulation and has as a postdoctoral fellow made several important contributions to the research field resulting in first-author publications in Cell (2000, 2002) and Genes and Development (2006). The committee notes that the group leader has published only 1 paper since 2003 (Genes Dev., 2006).

In the proposed research project, the group leader wishes to extend the analysis of CPEB in translational regulation using a combination of cell biology, biochemical and transcriptome profiling and to study the involvement of CPEB in human cancers. Towards this, preliminary data sustaining the research plan have been

obtained. In addition, the proposed research project involves collaborations already established within the institute.

Whereas the committee finds the research proposal to be scientifically sound and aimed at elucidating important biological mechanisms, it wishes to express two points of concern: 1) The proposal is highly dependent upon the success of the group leader in obtaining funding for the hiring of additional personnel. 2) The future success of the research group is crucially dependent on the availability of pre-existing mouse models for CPEB.

Nom de l'équipe : Study molecular mechanisms of cpeb-dependent translational 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

The unit is managed by a Director who is dedicated and science-driven. The organisation of the unit and its chart with the different responsabilities are well structured. Several of the researchers in the unit take responsibility for specific general tasks. One person, for instance, has been implicated in helping out with international grants. This has facilitated the obtention and management of several European grants.

The scientific communication within the unit seems good, with weekly lab meetings and journal clubs in which all people of the unit can participate. Communication with other units and institutes seems to be less optimal and could be improved (see below).

The unit is allocated with sufficient high-level technical and administrative staff, in particular when one considers that two of its senior researchers are no longer involved in practical science, but dedicate most of their time to the organisation, administration and external communicaton of the unit. In addition, the unit has a newly recruited staff member dedicated to bio-informatics.

6 • Recommendations and advice

- Strong points :

The strength of the unit lies in the quality of its research and in the inspiring, science-driven management by its Director. The committee considers favourably the unit's scientific output during the last four years. It notes that the research of the Director's group is of high impact and well-known internationally. The committee has confidence in the future research of this unit. It is also supportive of the shift in emphasis presented in the unit's research programme (stressing the role and regulation of small RNAs).

- Points to be improved :

The committee noticed aspects that require attention in the future. These points concern the structure of the unit, and the integration of the unit in the context of the Institute, the IFR and the campus as a whole. The unit in its past and present form has had several group leaders who were originally in the group of the unit head. This raises the question as to the independence of these junior groups. Independence could be perceived as a concern when one considers the past publication record of the unit where the unit leader is signing many papers from other supposedly independent research teams that were part of the past unit. Movement of teams outward and inward the unit is strongly encouraged to ensure scientific diversity and dynamics in the scientific production.

In addition, the committee feels that the situation of the unit and its communication with its direct environment could be improved, in particular to enhance broader interactions between students, postdoctoral reseachers and technical staff. An additional concern are the limitations in the housing and use of the mouse lines of the groups. Conditions seem sub-optimal for housing mice to which the researchers and students can have direct access. Although sophisticated equipments (FACS cell sorter, confocal microscopy etc) are available to the unit, they are at present not managed by allocated skilled personnel. Regrettably, the unit also no longer has access to a Stores which orders and dispatches consumables and chemicals. Solving these problems would require local re-organisation of technical staff/researchers rather than recruitment of new technical personnel.

- Recommendations :

The committee encourages the unit to pursue its complementary and interactive research projects. Given its current small size (four groups only, of which two starting groups) though, the committee recommends the unit to work towards attracting additional groups during the years to come. This would increase the critical mass and dynamics of the unit. New independent group leaders should be recruited externally, from elsewhere in France or abroad. The committee encourages the unit and its local partners to re-allocate technical staff to specific tasks and equipments (eg, to set up of an efficient Stores service). Furthermore, it encourages initiatives that improve access/usage of the mouse facilities by the unit, since this may have a limiting impact on the unit's future success. Finally, it advices the unit to improve communication with other groups in the institute and in the surrounding institutes on the campus. Such initiatives can only be achieved together with the local partners and would benefit the training and well-being of students and post-doctoral researchers, and of temporary and permanent staff of the unit.

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

UNIVERSITÉ
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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. : 99/09/GCo/LM/LS

Objet : Rapport d'évaluation d'unité de recherche
N° S2100012398

Monsieur le Directeur,

Vous m'avez transmis le onze mars dernier, le rapport d'évaluation de l'unité de recherche « Génétique fonctionnelle de la prolifération et de la différentiation cellulaire » - FRE 2944, et je vous en remercie.

L'université prend bonne note de l'appréciation et des suggestions faites par le Comité.

Les points à améliorer seront discutés avec le directeur d'unité dans un esprit constructif pour l'avenir de la recherche à l'université.

Vous trouverez en annexe les éléments de réponse de madame Annick HAREL-BELLAN, Directrice de l'unité de recherche.

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

Guy COURRAZE
Président

P.J. : Commentaires de Mme HAREL-BELLAN

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24/03/09

Comments from FRE 2944 on the AERES report.
The members of the FRE 2944 wish to thank the committee for their very constructive and helpful remarks and suggestions. We will, or have already, taken action to meet the recommendations of the committee as follows:
Concerning Team 1, the importance of delivery is acknowledged by the group leader, who has already set up a collaboration to address this issue in the framework of an "Innabiosanté" grant funded for 3 years. The limits of the xenografted mouse model are also acknowledged, and Team 1 has started clinical trials in other mammalian models in collaboration with the "Ecole Nationale Véterinaire".
Concerning the high-throughput RNAi platform, we do understand the concerns of the committee. Note, however, that, in its current state, the platform has 14 projects started or about to be started, corresponding to collaborations with 11 different labs and covering at least 18 months of work. We would like to add that, in our opinion, the future of this platform depends essentially on the appointment of permanent personnel and on the ability of the staff to keep up with this rapidly evolving technology.
Concerning Team 3, we would like to point out that the group leader obtained his/her PhD outside of the lab (and outside of the country) and thus, his/her promotion does not, in our opinion, fully qualify as an internal promotion. Along the line of the committee's suggestion, Team 3 is about to submit a completely independent paper. Also note that this paper, and the future research projects of Team 3, are entirely based on original ideas of the group leader, and do not in any manner correspond to a follow-up of his/her post-doctoral work in Team 2.
Concerning Team 4, the importance of the mouse model is indeed acknowledged. This model is available, and will be used in collaboration with the group leader's former lab, where this model was generated.
Concerning the important issue of the independence of the Teams in the lab, we would like to emphasize that the Teams are fully independent, in particular concerning their scientific strategy. It is the policy of the lab that signatures of papers correspond to actual participation in the work. Thus, the high number of papers signed by members of different Teams solely reflects real collaborations between these Teams.
Finally, concerning the integration of our Lab in the Institute:

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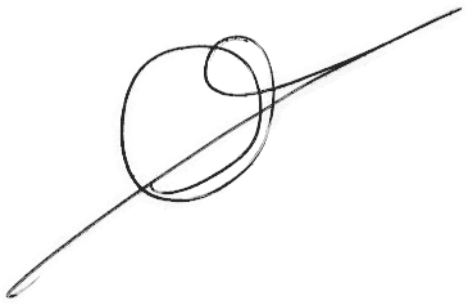
- Firstly, following the advice of the committee, actions have been taken to improve communication between the labs of the Institute:
1- An association of Young scientists (called YELL) has been created, essentially as an initiative of a PhD student from our lab. This association has been promoted and supported by the communications officer of our lab, who is also managing the communications bureau (BACS) of the André Lwoff Institute (IAL). The first meeting was held on February 27, 2009.
2- Following the initiative of the director of our lab, the Institute organized a meeting (February 2009) called "Première Rencontre Recherche Translationnelle IAL-Hôpital Paul Brousse" at the Centre Hépatobiliaire of the hospital. The purpose of this first meeting was to initiate communication between IAL and H. Paul Brousse research teams, in order to encourage collaborations.
3-The communications officer of our lab is currently organizing the first Meeting for Young IAL Scientists ("Journée des jeunes chercheurs de l'IAL"). Although open to every member of the Institute, the poster and oral presentations of the meeting are restricted to students and young post-docs. The purpose of this event is to improve the internal scientific communication among the young members of IAL, and to provide them with an opportunity to train and improve their communication skills. This meeting is scheduled for October 14, 2009.
- Secondly, we fully agree with the committee's comment on the lack of personnel to run the technical facilities of our Institute, and we will attempt to initiate a reorganization of the technical staff in the whole Institute. We are not totally convinced, however, that this problem can be solved simply by such a reorganisation. Only permanent staff – and they are not so numerous – can be redeployed in such a manner, the others being supported for specific projects. In addition, operating a mass spectrometer requires highly trained personnel and, in our opinion, can hardly correspond to a part-time job. As another example, animal care does not quite correspond to the skills and competence of the technical staff currently in the laboratories of the Institute.



Annick-Harel Bellan, Ph. D., DR1 CNRS, Directrice de le FRE 2944