UMR INRA ENVA de génétique 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 :

Génétique fonctionnelle et médicale

of the Ecole Nationale Vétérinaire d'Alfort

March 2009

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et de l'enseignement supérieur

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Evaluation report

Research unit :

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of the Ecole Nationale Vétérinaire d'Alfort

Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

mars 2009

Evaluation report

The research unit :

Name of the research unit : Génétique fonctionnelle et médicale

Requested label : UMR ENVA-INRA

N° in case of renewal : 955

Head of the research unit : Mme Geneviève AUBIN-HOUZELSTEIN

University or school :

ENVA

Other institutions and research organization:

INRA

Date of the visit :

February 16th, 2009

Members of the visiting committee

Chairman of the commitee :

M. Robert BALLOTTI, University of Nice-Sophia Antipolis

Other committee members :

M. Merete FREDHOLM, University of Copenhagen, Danmark

M. Goran ANDERSON, University of Uppsala, Sweden

M. Tosso LEEB, University of Bern, Switzerland

M. LLuis MONTOLIU, Campus de Cantoblanco Madrid, Spain

M. Bernhard WEHRLE-HALLER, University of Geneva, Switzerland

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

M. Jean-Luc VILOTTE, représentant des CSS de l'INRA

Observers

AERES scientific representative :

M. Philippe BOUVET

University or school representative :

M. H. BOULOUIS, ENVA representative

Research organization representative :

M. Didier BOICHARD, INRA representative

1• Short presentation of the research unit

- Total numbers of lab members : 23 including
  - 2 full time researchers
  - 7 researchers with teaching duties: 2 PR and 5 MCF
  - 3 PhD students, all funded
  - 10 engineers and technicians (9 INRA, 1 ENVA), 4 with part time employments (2 at 80% and 70%, 2 at 50%)
  - 1 administrative assistant (INRA)
- Number of HDR : 2
- Number of PEDR: 0
- Number of publishing lab members: 8 out of 9

This Unit is located in the Veterinary school at Alfort (Paris). It benefits from own mouse facilities and from a strong dog clinical recruitment at the Alfort campus. However, technical facilities or platform (imaging, proteomics, transcriptomics) are not available locally, but the Unit has a strong interaction with INRA at Jouy-en-Josas and with the Institut Pasteur that guarantees an easy access to all these methodologies and equipments.

The 3 research axes are focused on the study of (1) neurologic, muscular and cardiovascular diseases, (2) melanocyte- and melanoma stem cells and (3) genetic and environmental determinism of the intestine lengthening. This is clearly a multidisciplinary project, but federated by a functional genetics approach in both dog and mouse models.

2 • Preparation and execution of the visit

From 9h30 to 10h00, the Committee members and AERES representative had a close-door meeting. During 20 minutes, the former head of the laboratory summarized the past activity of the Unit. Then, from 10h30 to 13h, 6 researchers presented recent published and unpublished data and briefly exposed their projects, encompassing the three research axes of the applicant Unit. The candidate director closed the morning session by a digest of Unit's self assessment, organisation and expectations.

The afternoon, started with a visit of the laboratory. Then the committee successively discussed freely with the technicians, the students and the staff scientists and finally, the candidate director. These discussions were followed by a meeting with ENVA and INRA representatives. The visit was ended by a 45 min close-door meeting of Committee members, to complete the assessment form and to examine the critical points that emerged during the visit.

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

The committee was favourably impressed by the quality and the originality of most of the projects presented by the researchers. Although all the projects are based on similar approaches using dog and mouse genetics, the committee members noticed that the number of projects seemed to be overambitious according to the size of the Unit and in respect to the aim of creating an internationally recognized research unit. Indeed, each of the three research axes (see above) contains two different projects, meaning that six projects are intended to be developed in this unit.

The quality of the publications is within the average. The unit has published 20 articles during the last four years, 11 as first or last author (58 citations). The impact factors range from 0.98 to 10.8 (Blood, work not done in the laboratory). Most of the publications have an impact factor between 3 and 5. The most significant publications resulting from the Unit's projects are a Hum Mol Genet of 2005 (IF 8- 28 times cited) and a J Invest Dermatol (IF 4.5- the best journal of dermatology) of November 2008. These two publications, that respectively described the mutation

of PTPLA in centronuclear myopathy of the Labrador and the role of Notch/RBP-J in melanocyte stem cell biology, constitute the most outstanding results obtained by the unit during the last four years.

The Unit has two patents and one with license, demonstrating the high valorisation potential of the project. Most of the staff scientists have obtained grants as PIs, and only one of them is coordinator in an ANR projects. The Unit has initiated national and international collaborations within the European FP6 EuroTrans-bio and FP7 LUPA consortium (Dog genetics).

The committee has appreciated the enthusiasm and the dynamism of the researchers. This young unit could benefit from the international reputation in the field of its former director who will be now the scientific director of the unit. All categories of personnel have expressed their support to the new unit's organisation and to its new director.

It should be noted that 7 of the 9 staff scientists have heavy teaching duties and spend only 40% of their time in research.

Finally, both ENVA and INRA representatives have expressed their upmost support to the Unit.

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

Axe 1 : Genetics and pathophysiology of neurologic, muscular and cardiovascular diseases.

The projects developed in this axe will use mainly dog genetics to characterize gene mutations that cause neuronal ceroid lipofuscinosis (NCL) and centronuclear myopathy.

Concerning the centronuclear myopathy, the genetics approach that was used to identify PTPLA as the causative gene has been completed by a convincing approach using molecular and cellular biology. Function of PTPLA (protein tyrosine phosphatase-like) will be further investigated using pertinent mouse and cellular models.

The Unit has identified ARSG (Arylsulfatase G) as the gene mutated in neuronal ceroid lipofuscinosis in dogs. The role of ARSG will be investigated in human cases of NCL with unknown mutation.

These projects are linked to the European LUPA FP7 consortium in which the Unit is in charge of recruiting dogs with diseases relevant to human diseases, in specific relevant LUPA work packages. Further efforts will be made to identify genetic risk factors for canine cardiovascular disease using genome-wide association mapping, a method with high potential of success.

The committee has been favourably impressed by these projects that benefit from a very large dog recruitment and the will of the researchers involved in the projects to complete the functional analysis of the identified genes by using mouse and cellular models.

Axe 2 : Melanocyte and melanoma stem cells.

Using the patchwork mice (mice with black and white hairs), the unit has demonstrated the role of Sbno2 (Strawberry Notch homolog 2) in this phenotype and involved the Notch pathway in maintenance of melanocyte stem cells. Molecular and cellular biology approaches will be used to further characterize the role of the Notch pathway in melanocyte stem cells. Additional mouse mutants with pigmentation defects will also be studied to better understand melanocyte stem cell biology.

A second project will evaluate the role of RACK1 in melanoma development. Initially identified in pigs as melanoma marker, RACK1 has been found in human melanoma, but is absent in normal human melanocytes. Using modern technologies (Lentiviral shRNA delivery, in vivo confocal imaging), and also mouse models, the project will evaluate the role of RACK1 as a melanoma susceptibility gene.

The committee has appreciated these projects that used original animal models to better understand physiology of melanocytes and melanoma development. The committee feels that these projects have high potential and can be qualified as cutting-edge projects since they open new research avenues.

Axe 3 : Genetic and environmental determinism of intestine lengthening in PRM/Alf mice.

This project aimed to understand the mechanism of intestine lengthening in PRM/Alf mice. The following two hypotheses will be evaluated: 1) the role of microbiota and 2) the role of maternal milk. These studies involve analysis of intestine wall transcriptome and milk proteomic.

Another project will study the interstitial cell of Cajal and the contractile activity of the uterus in the PRM/Alf mice.

Although, the projects proposed in this axe are potentially interesting, the committee is less enthusiastic and confident in the feasibility of these two projects. The interactions with the other projects of the Unit do not appear clearly nor the rationale of the experiments proposed. Further these projects will be conducted by 2 researchers with teaching duties (0.6 full-time equivalents).

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

Space, equipment and budget of the laboratory are compatible with the proposed project. However, common facilities and technical platforms are not located on the Alfort campus. The Unit possesses its own mouse facility, but all the expenses related to mouse facilities are paid by the running budget of the Unit.

The researchers, the technicians and the students of the Unit seem happy working within the lab and are proud of their accomplishments. They support the new Unit organisation as well as its new director. This reflects the stimulating intellectual environment existing within the Unit.

6 • Recommendations and advice

- **Strong points :**

The Unit is composed of young, enthusiastic and dynamic researchers, and has an invaluable expertise in animal genetics, specifically dog and mouse genetics. They have access to a precious dog cohort recruited by the Alfort veterinary clinic and to a unique mouse coat-colour mutant collection. Their expertise gives the opportunity to rapidly transfer the knowledge gathered with dog models to functional studies using genetically engineered mouse models. The combination of dog and mouse genetics and the possibility to manipulate the mouse genome by the generation of new genetically modified mouse models is a unique feature and a distinctive achievement of this unit.

Recent data obtained in dogs (NCL, CNM) and in mouse (Sbno2) open the way for new research areas relevant to human physiology and pathologies.

The Unit is strong in Animal Genetics and Melanocyte Stem Cell Research and, therefore, these are the two main projects where its achievements are expected to be more relevant.

- **Weak points :**

The oversized number of projects according to the size of the Unit.

The heavy teaching duties of most of the staff scientists.

Despite being one of the most attractive units of the ENVA, the attractiveness of the laboratory for PhD students and post-docs remains low. The reduced number of PhD students within the Unit may be related to the fact that only one scientist can serve as main supervisor for PhD students (1 HDR).

Despite the evident qualities of the applicant director, the committee has not been completely convinced of her ability to focus the research of the Unit on the most promising projects.

There are many results not yet published, as recognised by the new Director of the Unit. Efforts should be made and priorities should be established to disseminate their achievements.

- **Recommendations :**

Optimize the use of the available technician resources. Currently, each technician is preferentially associated to each of the PIs in the group, with the exception of those working in the animal house. A more horizontal distribution of technician support to all the running projects would enable the group to increase their competitiveness. Of course, this reorganization should not abolish the friendly and stimulating working conditions existing within the Unit.

Recruit additional PhD students and post-doctoral fellows.

Focus on both melanocyte/melanoma and dog Genetics projects that appear to the committee as the most original and promising projects. The head of the Unit should evaluate the opportunity to discontinue the third project presented on intestine lengthening in PRM/Alf mice.

The committee has appreciated the will of the Unit to develop cellular biology approaches, but it has not been convinced that it will be possible for such a small Unit to perform both high quality genetics and cell biology. To be able to achieve high quality cell biology the Unit should recruit a senior expert in this field. Alternatively, the head of the Unit should consider the possibility to focus resources on genetics and molecular genetics, areas where the Unit has a strong and recognized competence. Cellular biology approaches might be performed in collaboration with external collaborators.

Although ENVA cannot improve its support in terms of budget or equipment, the committee suggests that ENVA should make an effort to reduce the teaching duties of the researchers. Similarly, it would be important that INRA increases its staff investment in the Unit.

UMR INRA ENVA de Génétique Moléculaire et 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
A	A	A	A	B

Ecole Nationale Vétérinaire d'Alfort

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A l'attention de Monsieur le
Directeur de la section des unités
AERES

Alfort le 26 mars 2009

Monsieur le Directeur,

Je vous prie de trouver ci-joint la réponse que la Directrice de l'UMR955 INRA-ENVA a souhaité vous transmettre. Cette réponse est organisée selon vos indications en deux fichiers attachés distincts, UMR955_général et UMR955_corrections.

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

Directeur Délégué à la Recherche
ENVA

UMR955 of Functional & Medical Genetics
Alfort School of Veterinary Medicine
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94704 Maisons-Alfort cedex FRANCE

Maisons-Alfort, March 26, 2009

Response to the report from the Visiting Committee, AERES

The UMR955 Unit is grateful to the Visiting Committee for their commitment during the visit and the constructive conclusions of their report. By enhancing the strength of combined dog and mouse genetics, recognizing the scientific quality of most projects and the dynamism of the researchers, the Committee encouraged us to proceed with the broad outlines of our proposed strategy for the future.

A point raised by the Visiting Committee is the overambitious number of projects regarding the size of the Unit. We are fully aware of this side effect resulting from the high number of relevant questions that have emerged in the last quadrennium. As already planned and according to the Committee's recommendation, the project dealing with the contractile activity of the uterus in the PRM/Alf mice, although with a high medical impact potential, will be closed after completion of the ongoing experiments and publication of the results. The project leader will then be able to increase her participation to the mouse and dog genetics projects that will benefit from her expertise in pathology.

Regarding the project on the genetic and environmental determinism of intestine lengthening in PRM/Alf mice, we are convinced of its high scientific potential. Accordingly, since the Committee visited our Unit, an article signed by the project leader as last author has been accepted for publication in the *Journal of Physiology and Pharmacology* (impact factor 4.47). Moreover, the project is led by a teacher-researcher of the Unit who is the principal investigator (PI) of a 3 years ANR ALIA project which started at the beginning of 2009 and involves both national and international collaborations.
The project emerged in our Unit with the genetic determinism of the phenotype. It now combines microbiology and proteomics in addition to genetics and as a consequence, it is presently carried out in three different INRA laboratories. The question of its homing in our Unit will be carefully re-considered at the end of the ANR ALIA project in December 2011 depending on its requirements in genetics, emphasized by the Committee as the strongest competence of our Unit.

The percentage of time that teachers-researchers dedicate to their research is presently a matter of debate in France and we do agree that it should be increased for those involved in long-term coordinated projects. To help the teachers-researchers, we have requested post-doctoral fellowships in our 2009 grant applications and will reiterate permanent staff positions requests to our administration.

The limiting factor for recruiting more PhD students is clearly the lack of HDRs, as quoted by the Visiting Committee. Indeed, the laboratory is well considered by undergraduate students with an average of 6 candidates for one position as master student trainee. To be able to offer more PhD positions, 4 researchers will pass their HDR by the end of 2009 while 3 others aim at defending their HDR by the end of the quadrennium.

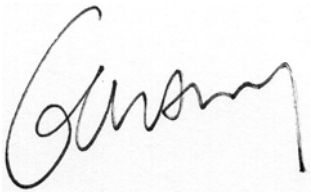
Besides we consider that our projects have matured enough to welcome post-docs and accordingly we have included post-doc salaries in the two last ANR projects deposited and will systematically do so in the future ANR proposals.

The Committee recommends either recruiting a senior scientist expert in cellular biology or developing collaborations with laboratories in the field. We consider that both recommendations are already partially met. We will benefit from the skills of our recently recruited teacher-researcher who did her PhD and post-doc research in prominent cellular biology laboratories. In parallel, specific collaborations have already been initiated with expert laboratories in France and the United Kingdom.

Finally, it is true that each technician preferentially follows one research project, mainly because our administration encouraged this working organization. However, every technician has developed specific personal expertise which is shared between projects. Moreover, we have just submitted a profile for a technician recruitment that includes more horizontal skills.

On behalf of the UMR955

Dr Geneviève Aubin-Houzelstein



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