MCPN - Mécanismes centraux et périphériques de la neurodégénérescence

Rapport Hcéres

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

Research Units Department

AERES report on unit:

Mécanismes Centraux et Périphériques de la Neurodégénérescence
(Central and Peripheral Mechanisms of Neurodegeneration)
U692

Under the supervision of the following institutions and research bodies:

INSERM

Université de Strasbourg

February 2012

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

Research Units Department

President of AERES

Didier Houssin

Research Units Department

Department Head

Pierre Glaudes

Unit

Name of unit:	Mécanismes Centraux et Périphériques de la Neurodégénérescence (Central and Peripheral Mechanisms of Neurodegeneration)
Acronym of unit:	
Label requested:	
Present no.:	U692
Name of Director (2009-2012):	Mr Jean-Philippe LOEFFLER
Name of project leader (2013-2017):	Mr Jean-Philippe LOEFFLER

Members of the committee of experts

Chair:	Mr Emmanuel BROUILLET, Fontenay-aux-Roses
Experts:	Mr David BLUM, Lille
	Mr Geert CALLEWAERT, Kortrijk, Belgium
	Ms Valérie FENELON, Bordeaux (CNU representative)
	Mr Stéphane HUNOT, Paris
	Mr Marc SAVASTA, Grenoble (CSS INSERM representative)

Representatives present during the visit

Scientific Delegate representing AERES:

Mr Christian GIAUME

Representative of the unit's supervising institutions and bodies:

Ms Catherine LABBE-JULIE, INSERM

Report

1 • Introduction

Date and conduct of visit:

The on-site visit lasted one day on February 15, 2012. It started at 8:30 am and ended the same day at 5:30 p.m. In the morning, committee members listened and questioned the head of the laboratory. Then, the committee members listened and questioned the researcher in charge of the theme "central aspects of ALS" and, later, the researcher in charge of the theme "peripheral aspects of ALS. This was followed by a short presentation by a young post-doc researcher on lipid metabolomics analysis methods. After lunch, the committee members and the AERES representative had a closed-door meeting with the supervising institutions representatives (University of Strasbourg – UDS-, Faculty of Medicine and INSERM). This was followed by a presentation of the research theme "biomarker". Then, the committee members separated in three groups. The first group met PhD students and postdoctoral fellows, the second engineers, technicians and administrative assistants, and the third one, researchers with a permanent position.

There was a closed-door final meeting (2 hours) with the committee members and AERES representative to gather the final opinion of the reviewers on the different criteria of evaluation. During this closed door meeting the committee has interviewed the director of the unit on specific points in relation with the presentations of the day.

Before the on-site visit, Chairman of the Committee has asked the experts to have a global analysis of the lab and send a written synthetic review on the lab activity and project with explicit questions to be prepared for the on site visit. At the end of the closed-door meeting, it was agreed that a first draft based on expert discussion would be written by the Chairman. This draft report was amended according to the suggestions and remarks of the members of the committee in order to reach a con sensus.

History and geographical location of the unit, and overall description of its field and activities:

U692 is an INSERM unit created in 2001. The U692 is located in the campus of the Faculty of Medicine of Strasbourg. U692 has been renewed as a single theme INSERM/UDS unit in 2009. The unit which gathers researchers and clinicians aims at better understanding the mechanisms of neurodegeneration in neurodegenerative diseases, including Amyotrophic Lateral Sclerosis (ALS) and Alzheimer's disease (AD), in order to find novel diagnostic tools and therapies. The entire Unit now focuses especially on ALS for the 2013-2017 research project. The Lab has planned to move into a new building at the Faculty of Medicine dedicated to translational research in 2014 (Biomedicine Research Center of Strasbourg).

Management team:

U692 is headed by J-P LOEFFLER since 2001. He will be the director of the Unit for the next five years. The project unit will be a single theme Unit with different research axis centered on ALS: 1) "central mechanisms of ALS", coordinated by a young INSERM researcher 2) "peripheral mechanisms of ALS", coordinated by the director and 3) "global approaches to the mechanisms of ALS and biomarkers" coordinated by a young associate professor holding a "Chaire d'Excellence" at University of Strasbourg.

Unit workforce:

Workforce	Number on 06/30/2011	Number on 01/01/2013	2013-2017 Number of producers**
N1: Professors or assistant professors	4	4	4
N2: EPST or EPIC researchers	3	2	2
N3: Other professors and researchers	2	2	2
N4: Engineers, technicians and administrative staff *****on a permanent position	4	5	
N5: Engineers, technicians and administrative staff ***** on a non-permanent position	2		
N6: Postdoctoral students having spent at least 12 months in the unit	0		
N7: Doctoral students	4		
N8: PhD defended	6		
N9: Number of Habilitations to Direct Research (HDR) defended	2		
N10: People habilitated to direct research or similar	5	6	
TOTAL N1 to N7	**19**	**13**	**8**

* **If** different, indicate corresponding FTEs in brackets.

** Number of producers in the 2008-2011 period who will be present in 2013-2017.

Definition and downloading of criteria:

http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

2 • Assessment of the unit

Overall opinion on the unit:

This is a very good research unit in the field of preclinical neurosciences and in particular in the ALS ground. The committee acknowledged the very good scientific production of the unit with very good publications in high impact factor journals, the strong scientific leadership and management of its director, the enthusiasm of the lab members and the cohesion between researchers and other collaborators. The activity of the unit is associated with unquestionable international recognition and excellent integration in the local environment, especially the UDS. The scientific project, which tackles key questions in ALS physiopathology, linked to dyshomeostasis of energy metabolism includes many highly innovative aspects and is very ambitious. Importantly, the preclinical research project has a real clinical counterpart with high potential for discovery of novel pathways involved in ALS pathogenesis, translational perspectives, in particular discovery of ALS biomarkers, and proof-of-concept of novel therapies.

Strengths and opportunities:

The future research project is now clearly focused on ALS. This reorganization has the great advantage to stimulate a synergy between all researchers and help to build a scientifically coherent unit.

The unit has an international recognition and is integrated in national and international networks dedicated to the deciphering of ALS pathogenesis.

The unit has young dynamic theme leaders and there is an opportunity to recruit a new and young research scientist in the next 1-2 years.

The unit will benefit from an excellent scientific and technical environment around Strasbourg (technical facilities and services, IDEX of UDS).

The building of a new center (Biomedicine Research Center or BRC) to gather clinical and research activities is seen as a good opportunity for more efficient research since the BRC should offer access to mutualized services and platforms (especially animal facility) and should facilitate interactions with clinicians and researchers from other labs.

The foreseen financing for the first part of the program is satisfactory with a FP7 call grant (→ 2015), a "junior" ANR research grant (→ 2014) and a PHRC project on biomarkers that has been recently accepted (→ 2015). In addition, a contract of collaboration with the pharmaceutical company Servier has been recently signed that will give access to a metabolomic platform.

There is an excellent management and interaction between the different members of the unit (including technicians, engineers, PhDs and postdocs).

Weaknesses and risks:

The project is very ambitious and some aspects might not fulfill unit expectations if manpower is not significantly increased, in particular to stabilize technical know-how.

The transversal "biomarker" research theme in the unit might not have the necessary size and development for reliable, fully validated identification of diagnostic tools for ALS, although it will be likely successful for identification of "mechanistic" hypothesis for further studying ALS pathogenesis.

Recommendations:

The committee recommends that all effort should be made to recruit young investigators (post-doc and permanent position) to reinforce the manpower for the three research themes. Similarly providing a permanent position to technicians involved in animal research should remain a priority to perpetuate the known-how related to preclinical aspects of the project.

Considering the strong international competition on biomarkers in the field of neurodegenerative diseases, the committee has come to the conclusion that this part of the project may be "too large and a little hazardous". Indeed, the committee considers that the rate of success in identifying, but most of all, validating new diagnostic and/or prognostic biomarkers is relatively low given the small cohorts of patients available so far. Furthermore, the clinical aspects of the biomarker project (especially validation of biomarkers) may need complementary approaches (imaging, genetics, and wider cohort) to remain fully competitive. Yet, the committee acknowledges the usefulness of such approaches to identify and characterize new potential pathogenic pathways that should then be validated through hypothesis-driven mechanistic studies at the preclinical level. Accordingly, the committee strongly recommends strengthening this latter aspect of the biomarker program.

3 • Detailed assessments

Assessment of scientific quality and production:

Research on neurodegeneration in the past 4 years has shown real originality with high impact on the international community.

Very good activity is demonstrated by a large number of recent publications in peer-reviewed journal including several high impact factors journals (EMBO, J. Neuroscience, PNAS, Hum Mol Genetics, Lancet Neurol), creation of a spin off biotech, and patents. The ratio of "publication number" to the number of publishing researchers for the past four years is good (66/8).

Assessment of the unit's integration into its environment:

U692 research has led to the creation of a spin-off biotech and 3 patents. One important aspect of research transfer for U692 is the clinical research/applications (biomarkers) and therapeutic assays based on preclinical and clinical data obtained by the group.

In addition to specialized publication, team members have been involved in different actions promoting science to broad audience.

All researchers and professors of the lab are involved in student training and evaluation committees (thesis, master) and play a key role in Master 2 teaching.

U692 has strong link with host institution (UDS Lab members including the director have responsibilities in UDS scientific committees and councils.

In addition, the lab has developed strong partnership with industry (signed contracts of collaboration with Servier).

U692 obtained several financial supports form competitive calls (FP7, ANR) and Foundations.

Assessment of the research unit's reputation and drawing power:

Researchers of the U692 are regularly invited to give conferences abroad in international meetings and editorial committees.

The head of the unit has an unquestioned international visibility in the field of ALS.

The lab has shown a good recruitment dynamics (several post docs and PhDs, 1 chair of excellence Professorship, 1 INSERM Engineer). In addition, two CNRS researchers were promoted and started their own team.

U692 has set up strong collaborative link with European countries through a FP7 consortium. In addition, one of the PI has a "Mercator" professor position in Ulm where he conducts clinical researches.

Assessment of the unit's governance and life:

The lab is well structured for decision making through meeting between the director and theme leaders and downstream all members of the lab including engineers and technicians. Scientific meetings are also organized to promote scientific exchanges within the lab. The committee has acknowledged the existence of good relationship and conviviality between lab members that create a real synergy.

Emergence of young investigators toward leadership has been promoted. The student training, management and follow-up seem to be excellent. One former PhD currently in post-doc abroad (Harvard Medical School) applied for a CNRS position and was very well ranked in 2011.

Team members are involved in local educational/teaching activities (USD) and European courses (FENS). In addition they sit in different Masters' committees and decision-making boards of the university.

Assessment of the strategy and 5-year project:

The 5 years project is based on a strong background and solid published data. It is an innovative research project focused on ALS mechanisms linked to energy metabolism dyshomeostasis. Development and analysis of novel animal models of ALS are planned and the on-site visit allowed the committee to testify that the study of these original models is already ongoing with success. The project remains focused on the original hypothesis that energy metabolism dyshomeostasis is likely involved in ALS pathogenesis. The director and his collaborators were pioneers in suggesting such hypothesis years ago and are therefore leader in the field. The lab researchers have sufficient expertise and creativity to remain surfing on the top of the wave in the competition with other groups working on the same line.

The project presents several original aspects of the research at the cellular and preclinical levels. It is both qualitatively and quantitatively ambitious but stays realistic in scope on several aspects. Yet, the adjunction of full-time researchers and technicians appears crucial for the sake of success. Overall, research projects following up on previous achievements on one hand, and new, innovative risk-taking line of research on the other hand are well balanced. Yet, although the biomarker approach will likely lead to interesting hypothesis related to the pathogenesis of ALS, the clinical aspects of this project line, (transversal in the lab) need to be embedded in a larger consortium with broader approaches (including genetics and imaging) to remain fully competitive and to improve its feasibility.

Although funding for some research lines are not secured yet, several applications to competitive national (ANR/PHRC) and European (ERC) grants are ongoing. Furthermore, the lab policy is to "distribute" funds among researchers allowing some flexibility. Technical means (equipments) have been acquired in the last 4 years and for the future, and the researchers privilege the use of platforms/services.

Assessment of the unit's involvement in training:

All members of the lab offer high involvement in teaching at UDS and provide good training in the lab. There is an excellent follow up (good tutoring and mentoring) of students during masters and PhDs training and thereafter.

4 • Grading

Once the visits for the 2011-2012 evaluation campaign had been completed, the chairpersons of the expert committees, who met per disciplinary group, proceeded to attribute a score to the research units in their group (and, when necessary, for these units' in-house teams).

This score (A+, A, B, C) concerned each of the four criteria defined by the AERES and was given along with an overall assessment.

With respect to this score, the research unit concerned by this report (and, when necessary, its in-house teams) received the overall assessment and the following grades:

Overall assessment of the unit [Mécanismes Centraux et Périphériques de la Neurodégénérescence (Central and Peripheral Mechanisms of Neurodegeneration)]:

Unité dont la production, le rayonnement et le projet sont très bons. L'organisation et l'animation sont excellentes.

Grading table:

C1 Scientific quality and production.	**C2** Reputation and drawing power, integration into the environment.	**C3** Laboratory life and governance.	**C4** Strategy and scientific project.
A	**A**	**A+**	**A**

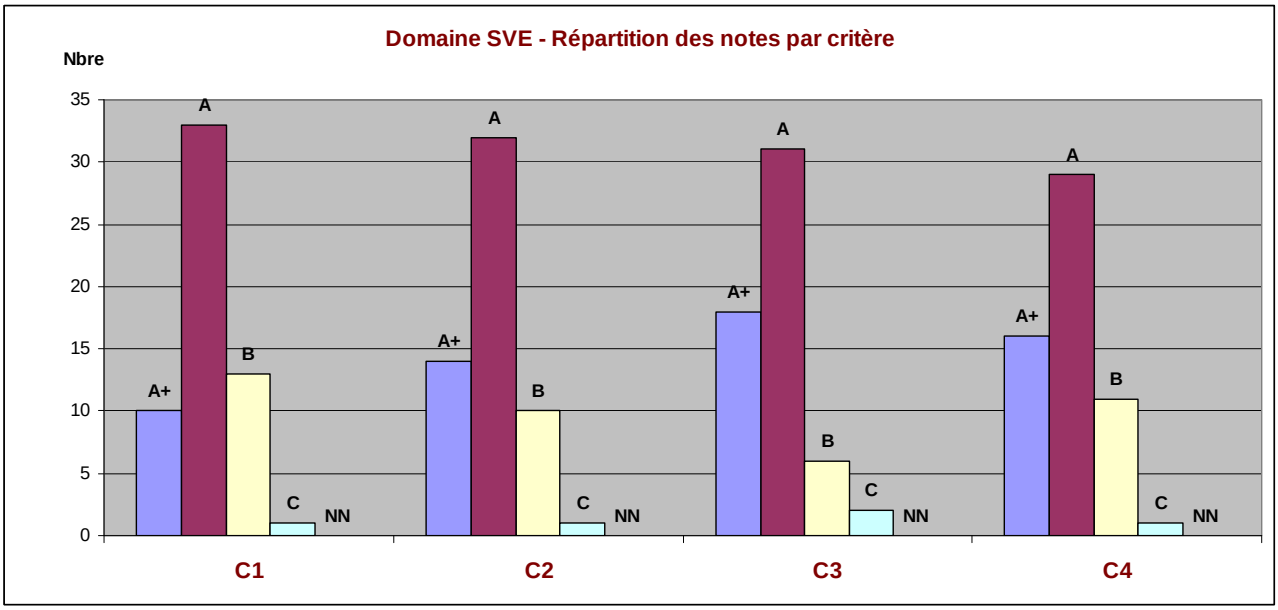
5 • Statistics per field : SVE au 10/05/2012

Notes

Critères	C1	C2	C3	C4
	Scientific quality and production	Reputation and drawing power, integration into the environment	Laboratory life and governance	Strategy and scientific project
A+	10	14	18	16
A	33	32	31	29
B	13	10	6	11
C	1	1	2	1
Non noté	-	-	-	-

Pourcentages

Critères	C1	C2	C3	C4
	Scientific quality and production	Reputation and drawing power, integration into the environment	Laboratory life and governance	Strategy and scientific project
A+	18%	25%	32%	28%
A	58%	56%	54%	51%
B	23%	18%	11%	19%
C	2%	2%	4%	2%
Non noté	-	-	-	-



UNIVERSITÉ DE STRASBOURG

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l'enseignement supérieur (AERES)
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Alain BERETZ
Président

Strasbourg, le 25 avril 2012

Objet : Rapport d'évaluation de l'UMR_S 692 Mécanismes centraux et périphériques de la neurodégénérescence (réf. S2PUR130004534-RT)
Réf. : AB/EW/N° 2012-199

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Direction de la recherche

Cher collègue,

Je vous remercie pour l'évaluation de l'unité mixte de recherche « Mécanismes centraux et périphériques de la neurodégénérescence » (UMR_S 692 Université de Strasbourg et INSERM) dirigée par Monsieur Jean-Philippe Loeffler.

Vous trouverez ci-joint les réponses du directeur de l'unité de recherche concernant les erreurs factuelles et les remarques et appréciations du comité d'experts.

Je tiens à préciser que les emplois vacants de personnels ingénieurs et techniciens (BIATS) permanents font l'objet, comme tous les emplois, d'un arbitrage au niveau de l'Université. Le dialogue de gestion instauré avec les composantes et les unités de recherche permet de dégager les priorités soit en terme de maintien d'emplois soit en terme de redéploiement d'emplois.

Je vous prie d'agréer, Cher Collègue, l'expression de mes sentiments distingués.

Alain BERETZ

P.J. :

- **Une première partie corrigeant les erreurs factuelles**
- **Une seconde partie sans observations**

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Strasbourg le 3/4/2012

Objet : évaluation par l'AERES

U692

Laboratoire de Signalisations Moléculaires et Neurodégénérescence

Monsieur le vice président, Cher Eric,

Veuillez trouver ci-dessous notre réponse au comité AERES.

Nous n'avons pas relevé d'erreurs factuelles, et vous communiquons donc un seul document qui rassemble nos observations générales, en particulier sur les 2 points mentionnés par le comité.

Vous souhaitant bonne réception,

Cordialement

Jean-Philippe LOEFFLER

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Observations générales sur le rapport d'évaluation du projet « mécanismes centraux et périphériques de la neurodégénérescence :

We acknowledge the members of the committee for their helpful and very positive comments on our Laboratory and project.

The committee raises two questions that would need further clarification:

1) The project is very ambitious and some aspects might not fulfill unit expectations if manpower is not significantly increased, in particular to stabilize technical know-how.

The Laboratory is aware of the increasing demand of manpower required for further develop our scientific objectives over the next years. This is why we have for some years now a strategy of attractivity. We dedicate much effort and available, yet limited, resources at developping new technical resources in order to attract new technicians and researchers. These actions have revealed particularly fruitful recently, since Michele Vogel, ingenieur d'études INSERM, joined the team to specifically develop AAV-based gene transfer approaches in our new L2 facility. Also, 18 months ago the improvement of our histology facility allowed us to attract Sylvie Dirrig-Grosch who is now in charge of this approach. In addition, two young technicians, Jérôme Sinniger and Thibeault Lequeu, were hired on projects granted by ANR and Servier, respectively, to implement our pre-clinical and clinical research axes. *Our priority in the next future will be to stabilize these currently non-permanent positions*.

In the context of our FP7 Euro-MOTOR contract, launched in February 2011, the Laboratory hired Alexandre Henriques as a post-doctoral fellow for 4 years to specifically strengthen the biomarker discovery axis of the team. We believe that such an experience will allow him to reinforce his scientific track-record in order to apply for a CR2 tenure position in the future. Finally, *Caroline Rouaux, who has spent 3 years as a post-doctoral fellow at Harvard University, is now under evaluation by the INSERM Neurosiences scientific committee to join our team as a young CR2 fellow*. It is noteworthy to mention that her expertise acquired at Harvard University on the development and maturation of cortical motor neurons (see for instance, Rouaux et al., Nat Neurosci, 2010) would be very valuable to consolidate our projects focused on the central pathogenic mechanisms underlying ALS. Caroline Rouaux obtained the fifth position in the ranking of the 2011 campaign, and has been pre-selected very recently to defend her project next May 2012.

In conclusion, we would like to stress out that the Laboratory is actively engaged in the recruitment of new personnel by offering the best available training and encouraging both researchers and technicians to compete for permanent positions. However, such a task cannot be accomplished successfully without the support of our hosting institutions, INSERM and University of Strasbourg.

2) The transversal "biomarker" research theme in the unit might not have the necessary size and development for reliable, fully validated identification of diagnostic tools for ALS, although it will be likely successful for identification of "mechanistic" hypothesis for further studying ALS pathogenesis.

Particular omics approaches (such as the search for polymorphic variants in the diseased versus healthy population) are usually planned in an unbiased manner, and hence depend on great cohorts of individuals in order to be able to identify robust changes. In contrast, the selection of patients in our omics studies is made on the basis of specific hypothesis-driven facts. For instance, this is the case of the study of the muscle transcriptome in patients with ALS, FTD or ALS/FTD, which is based on the observation that a high proportion of FTD patients will eventually develop symptoms characteristic of motor neuron disease. The size of the cohorts in these studies is limited by the facts that the number of available patients with FTD progressing towards ALS is small, and that obtaining muscle biopsies in this kind of patients remains invasive, and is not part of the work-up of the diagnostic process. As noticed by the committee, our omics studies have a strong potential to identify changes of mechanistic value, but we are also aware that they are not appropriate to go further into the validation of the identified biomarkers, which is a step requiring a large number of individuals. To circumvent this limitation, *we have ensured the access to such great cohorts in the context of the FP7 Euro-MOTOR consortium and through a direct collaboration with the University of Ulm*. These collaborations will provide us with the required validation of our hypotheses previously generated from our pilot experiments.