



Petites molécules de neuroprotection, neurorégénération et remyélinisation

Rapport Hcéres

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

Department for the evaluation of
research units

AERES report on unit:

Neuroprotection and neuroregeneration:
neuroactive small molecules

SMOREPAIR

Under the supervision of the following
institutions and research bodies:

Institut National de la Santé Et de la Recherche

Médicale - INSERM

Université Paris-Sud

December 2013



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

Department for the evaluation of
research units

*On behalf of AERES, pursuant to the Decree
of 3 november 2006¹,*

- Mr. Didier HOUSSIN, president
- Mr. Pierre GLAUDES, head of the
evaluation of research units department

On behalf of the expert committee,

- Mr. Serge TMSIT, chair of the committee

¹ The AERES President "signs [...], the evaluation reports, [...] countersigned for each department by the director concerned" (Article 9, paragraph 3 of the Decree n° 2006-1334 of 3 November 2006, as amended).

Evaluation report

This report is the result of the evaluation by the experts committee, the composition of which is specified below.

The assessment contained herein are the expression of independent and collegial deliberation of the committee.

Unit name: Neuroprotection and neuroregeneration: neuroactive small molecules

Unit acronym: SMOREPAIR

Label requested:

Present no.:

Name of Director
(2013-2014): Mr Michael SCHUMACHER

Name of Project Leader
(2015-2019): Mr Michael SCHUMACHER

Expert committee members

Chair: Mr Serge TMSIT, Université de Bretagne Occidentale, Brest

Experts: Mr Osborne ALMEIDA, Max Planck Institute of Psychiatry, Munchen, Germany

Mr Luis-Miguel GARCIA SEGURA, Instituto Cajal, Madrid, Spain

Ms Isabelle LIHRMANN, INSERM, Rouen (representative of CSS INSERM)

Ms Rhona MIRSKY, University College London, United Kingdom

Mr Denis VIVIEN, INSERM, Caen (representative of CNU)

Scientific delegate representing the AERES:

Mr Laurent GROC

Representatives of the unit's supervising institutions and bodies:

Mr Etienne AUGE, Université Paris-Sud

Mr Etienne HIRSCH, INSERM

Mr Michael SCHUMACHER (representative of the Doctoral School n° 419)

1 • Introduction

In 1998, Inserm Research unit 488 has been created under the responsibility of Mr Michael SCHUMACHER from the former unit U33, headed by Mr Etienne-Emile BAULIEU. The efforts of U488 were focused on the effects of steroid hormones on the nervous system, as indicated by its title "Steroids and the Nervous System". Only part of the researchers of the former U33, dedicated to endocrine research, accepted this thematic reorientation towards the neurosciences. In 2006, UMR 788 was created. In 2009, the research unit was for the first time evaluated by the Aeres agency, and changed again the title of the unit, which became "Neuroprotection and neuroregeneration: neuroactive small molecules". The unit became also part of the recently created LABEX "NeuroSclex", strengthening interactions with the different neurosciences laboratories of Paris-Sud, and in particular with the Alfred Fessard Institute (Gif-sur-Yvette). Recently, in May 2013, a researcher from the "Institute of Neurobiology Alfred Fessard", joined the research unit to create a new team in the field of myelination and myelin repair in the central and peripheral nervous systems. The laboratory is situated in the Bicêtre hospital.

Management team

Mr Michael SCHUMACHER will head the new research unit.

AERES nomenclature

SVE1_LS5 Neurobiology

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	6	8
N2: Permanent researchers from Institutions and similar positions	7	7
N3: Other permanent staff (without research duties)	11	11
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	1	1
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	5	5
N6: Other contractual staff (without research duties)	2	2
TOTAL N1 to N6	32	34

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	12	
Theses defended	4	
Postdoctoral students having spent at least 12 months in the unit*	3	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	11	13

2 • Assessment of the unit

It was obvious to the experts committee that all members of the unit are highly committed and enthusiastic about the future project. The presence of basic researchers and clinicians in the same unit is strength but increased basic-clinical dialogue will be important to guarantee success and productivity. At the same time, there is significant complementary expertise within the unit. Several patents have been filed by members of the unit, reflecting its dynamism and clear success to translate to the economic environment. The training of PhD students is of a high standard; the increased number of students and post-docs is a major asset for the future of the unit. The unit has obtained funding from collaborations with the pharmaceutical industry and a non-profit organization, but more basic research-related grants from national and European sources will help demonstrate competitiveness and increase research capacity. Interactions between the different teams and project leaders, sharing results, methodologies and technical expertise need to be maintained and further encouraged. Participation in and organization of high-level international meetings will ensure visibility and timely addition of leading-edge concepts and technologies to the unit's activities.

Strengths and opportunities:

The research unit belongs to the excellence initiative LABEX "Neurosclex. The whole unit already benefits from excellent training programs and is strongly committed to training the next generation of researchers. The arrival of a new team is strength and also an opportunity to better integrate basic research and clinicians. High level of expertise in the field of neurosteroid should be maintained.

Weaknesses and threats:

The scope of research should not be too large. Optimization of projects is proposed for team-1 (see below) and in the same time new interactions should be developed between team-1 and team-2.

Recommendations:

Develop strong interactions within each team and between teams on few defined projects. Greater integration of the clinical projects with basic projects is anticipated and recommended, thus strengthening the global mission of the unit.

3 • Detailed assessments

Assessment of scientific quality and outputs

The overall quality of publications at the unit level is considered excellent. The scope of publications is very large from basic research to more clinically oriented publications. The investigated fields include: stroke, surgical reconstruction after facial nerve and brachial plexus injury, treatment and early diagnosis of transthyretin-familial amyloid neuropathy, morphology and regeneration of the autonomous nervous system, dementia, myelination and myelin repair. Team 1 publishes in highly respected journals such as *Endocrinology*, which however do not have high impact factors but which serve at the interface between endocrinology and stroke. The level of team-2 publications is high with papers in high impact journals. Thus, the unit has produced good publications over the past 5 years, strengthening further its visibility in the field of neuroendocrinology. It should be mentioned, however, that the scope of research might be too large.

Assessment of the unit's academic reputation and appeal

The unit has been deeply modified: many people are retiring and others are arriving showing therefore the attractiveness of the unit. There is thus an opportunity to restructure the unit as a whole. The academic reputation of the unit in the field of neurosteroids has been very high for many years. Team-1 continues to enjoy high visibility at the international level; team-2 will undoubtedly build a strong reputation because it has published several very important papers in leading journals.

Assessment of the unit's interaction with the social, economic and cultural environment

As a whole the unit has filed patents. Interaction between members of the unit will certainly produce new intellectual property.

Assessment of the unit's organisation and life

Overall, all members of the unit (PhD students, engineers/technicians, and researchers) reported a high level of satisfaction, with good communication at all levels in the unit. The team leaders were happy with budget allocations, but the scientific committee would like to encourage researchers to strive toward greater individual excellence and professional development. The recent restructuring of the Unit, together with the foreseeable retirement and recruitment of new staff, provide an opportunity to improve focus, integration and productivity as well as sharing of technical know-how.

Assessment of the unit's involvement in training through research

The whole unit already benefits from excellent training programs and is strongly committed to training the next generation of researchers. The director of the unit has a lot of responsibility and dynamism concerning training. He is the director of the Doctoral School “Biosigne” (ED n°419) (see also below) and a “diplôme universitaire” in translational research has been created. Members of the research unit are involved in many teaching activities. A large number of continued training programs are followed each year by the personnel of the unit. Furthermore, 12 members will have the “Habilitation à Diriger des Recherches” (HDR). Eight of them can be expected to supervise PhDs during the next 5 years.

Meeting with the head of the école doctorale, who is the director of the unit, further emphasized the great involvement of the unit in the PhD school of the Université Paris Sud. Running such a “école doctorale” is a tremendous achievement and a clear asset for the unit since its students are well-educated of the training resources and potential. For these reasons, the unit personnel is fully and strongly dedicated to the training of graduate students at the Université Paris Sud, a remarkable dedication.



Assessment of the strategy and the five-year plan

The unit benefits from previous unique experience in the area of neurosteroids and the introduction of new models of disease. Therefore, there is high potential for teams 1 and 2 to achieve their individual goals, thus contributing to the overall goals of the whole unit. The knowledge and expertise of team-1 in neurosteroids will provide important support for team-2. Team-2 adds value to the whole unit, especially in the context of complementary expertise. Greater integration of the clinical projects with basic projects is anticipated and recommended, thus strengthening the global mission of the unit.

4 • Team-by-team analysis

Team 1: Neuroprotection and Axonal Regeneration

Name of team leader: Mr Michael SCHUMACHER and Ms Rachida GUENNOUN

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	5	7
N2: Permanent EPST or EPIC researchers and similar positions	5	5
N3: Other permanent staff (without research duties)	7	7
N4: Other professors (PREM, ECC, etc.)	1	1
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	3
N6: Other contractual staff (without research duties)	1	1
TOTAL N1 to N6	22	24

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	7	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	8	10

• Detailed assessments

Assessment of scientific quality and outputs

The team focuses on neuroprotection and axonal regeneration in 4 different projects: 1) steroid neuroprotection, 2) steroid profiling, 3) glycinergic and GABAergic inhibition of hypoglossal neurons mediated by neurosteroids, and 4) neuroregeneration, physiopathology and pain. This is a potentially important area of research. The team demonstrates a high level of expertise and unique methodologies (steroid analysis), which can facilitate identification of putative new agents for neuroprotection and/or to promote regeneration. Overall, the quality of the research production is very good. They have published more than 200 articles and 26 original papers in journals with

good impact factors since 2008 (33 publications with direct contributions). Numerous articles have been published in international journals that have reasonable impact factors, many of them are leading journals in the field (ex. PNAS, Brain, Endocrinology, J. Neuroscience). Studies concerning safety and efficacy of RNAi therapy for transthyretin amyloidosis were recently published in the New England Journal of Medicine by a member of the unit.

Assessment of the unit's academic reputation and appeal

The research unit belongs to the excellence initiative LABEX “Neurosclex”. The leaders are well-recognized researchers in their field of expertise, this from a long period of time. The team has an impressive number of 43 ongoing collaborations, 20 with French laboratories and 23 with foreign institutions. One team leader has acted as a referee for 36 international journals.

Assessment of the unit's interaction with the social, economic and cultural environment

The team has filed 3 patents and signed 8 contracts with private entities. A company that develops neurosteroid-derivatives for the treatment of CNS disorders is associated with the unit. The team has good interactions with industrial and clinical partners and a non-profit organization.

Assessment of the unit's involvement in training through research

The number of PhD students has increased in the last few years. The unit has welcomed 31 students at Master 1 and 2 levels and 19 trainees (PhD students, BTS, DUT, secondary school students). One of the team leaders is director of the doctoral school “Signalling and integrated networks in biology” from the Université Paris Sud. Within the framework of the doctoral school, the team initiated a course related to translational research (40 hours), which has now become a Diplôme Universitaire of the Université Paris Sud (100 hours).

Assessment of the strategy and the five-year plan

There were concerns about the number of projects using overlapping approaches. At present, Projects 1, 2, 3 and 4 appear to be insufficiently connected since too many disease states are addressed. There is also a lack of mechanistic insights. However, given the recent restructuring of the team, including incorporation of clinicians and new techniques, there is great potential to deliver new insights and potential applications (translational medicine).

Conclusion

▪ Strengths and opportunities:

The team-1 has a well-sustained high-level expertise in the field of neurosteroids and is a recognized international leaders in the field. There is great opportunities and potential to develop small molecules as drugs through intense collaboration with public bodies and private companies.

▪ Weaknesses and threats:

The presence of basic researchers and clinicians in the same unit is a strength but can be capitalized on through greater interactions in the future. The team should focus and expand mechanistic approaches on a smaller number of pathologies. Molecular and translational approaches should focus on the same chosen diseases.

▪ Recommendations:

The experts committee sees an opportunity for optimization of the team project. We recommend a better integration of different projects, such as collapsing the present 5 projects (1-4 + transversal project) into 3. It may lead to the combination of projects 1 and 2 (steroid and profiling), and integrate project 3 (electrophysiological studies) into project 4. Project 1 would become “steroid neuroprotection and profiling”, project 2 would become “neuroregeneration, morphology and pathophysiology”, project 3 (currently, “transverse project”) would become “dementia and neurodegeneration”. The members of project 3 who are funded by the Fondation would be hosted by the team.

Team 2: Myelination and myelin repair

Name of team leader: Ms Elisabeth TRAIFFORT

Workforce:

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1	1
N2: Permanent EPST or EPIC researchers and similar positions	2	2
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	2
N6: Other contractual staff (without research duties)	1	1
TOTAL N1 to N6	6	6

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	5	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	3	3

• Detailed assessments

Assessment of scientific quality and outputs

Team 2 have made fundamental and highly original contributions to the topic of myelination and myelin repair in recent years, identifying new unexpected molecular targets involved in myelin repair and development, including Sonic Hedgehog (Shh) signaling, Wnt/ β -catenin signaling, androgen receptor and progesterone receptor signaling. These findings, which have been published in leading scientific journals, have opened a range of new lines of investigation that have had considerable international impact in the field in terms of literature quotations. The group leader has published more than 60 papers in well-recognized journals (e.g. J. Neuroscience, FASEB J.).

Assessment of the unit's academic reputation and appeal

The team is a new one. This team has attracted members of team 1 of the current research unit, including two project leaders. Team 2 has maintained numerous national (9) and international (10) collaborations and has produced highly relevant scientific contributions to the field, further strengthening the reputation and appeal of the group leader.

Assessment of the unit's interaction with the social, economic and cultural environment

Members of the team have experience in technology transfer and have produced 2 patents. They are collaborating with non-academic partners, such as the non-profit Population Council (New York) and M&P Pharma AG, on:

I) the use of an androgen receptor agonist (7 α -methyl-19-nortestosterone; Nestorone®) to promote remyelination;

II) new formulations and methods to deliver small neuroprotective molecules (progesterone, progestins, Nestorone®) to the brain.

Assessment of the unit's involvement in training through research

The team members are actively involved in research training. They actively participate in the training of Masters and PhD students of the unit and in the Université Paris Sud. At present there are 5 PhD students in the team. Members of the team teach in a course (UE) at Master 1 level (Université Paris Sud), a program entitled "Initiation aux Neurosciences". It should be noted that previous PhDs have made a successful transition to the next step of their career.

Assessment of the strategy and the five-year plan

The five-year plan of the team is organized in 3 well-designed projects with clearly focused and complementary aims. There is clear synergy and complementarity between the 3 projects of the team, which gives this group a clear advantage over other groups in this area of research. The five-year plan of team 2 represents a very innovative and original approach to explore the mechanisms of central and peripheral myelination, with a clear focus on the identification of new therapeutic targets. In addition, team 2 has collaborations with non-academic partners, such as the Population Council (New York) and a pharmaceutical company to test practical applications. Given the previous experience and accomplishments of the members of the team, the five-year plan seems to be feasible.

Conclusion

▪ Strengths and opportunities:

The team-2 develops well focused projects that include mechanistic and translational approaches. The introduction of zebrafish to model disease has already benefited the whole unit. Close interactions with team 1 will bring mutual benefits (added value) to both teams and the unit as a whole.

▪ Weaknesses and threats:

Team leaders should make efforts to apply for dedicated funding, thus helping this new team's growth and development, including recruitment of technicians. This new team's strength will depend strongly on interactions between its three project leaders. Efforts to increase visibility at the international level through organization of focused symposia, research clusters, etc, is strongly encouraged.

▪ Recommendations:

The team has received much support from the unit during its establishment and this should be continued.

5 • Conduct of the visit

Visit dates:

Start: December 19th 2013 at 8:30 am

End: December 20th 2013 at 1:00 pm

Visit site: Hôpital Kremlin-Bicêtre

Institution: INSERM

Conduct or programme of visit:

December 19th 2013

08:30-08:45 am	Arrival at laboratory
08:45-09:20 am	Experts committee discussion (closed-door)
09:20-09:30 am	Welcome - presentation of the AERES (Mr Laurent GROC) and of the experts committee (Mr Serge TIMSIT)
09:30-10:15 am	Unit presentation by Mr Michael SCHUMACHER
10:15-11:00 am	<u>Team 1:</u> Mr Michael SCHUMACHER / Ms Rachida GUENNOUN (presentation + question)
11:20-12:05 pm	<u>Team 2:</u> Ms Elisabeth TRAIFFORT (presentation + question)
12:15-01:30 pm	Lunch (on site) with all lab members (for potential discussions)
01:30-02:15 pm	<u>Transversal project:</u> Mr Etienne-Emile BAULIEU
02:15-04:15 pm	Parallel meetings <ul style="list-style-type: none"> - meeting with students/postdocs - meeting with ITAs - meeting with researchers (without team leader and director)
04:45-05:15 pm	Meeting with tutelles
05:15-05:30 pm	Meeting with the head of the École Doctorale: Mr Michael SCHUMACHER
05:30-06:30 pm	Debriefing experts committee

December 20th 2013

09:00-09:45 am	Interview with director (closed door)
09:45-02:00 pm	Closed-door final meeting (lunch on site)
02:00 pm	End of the visit



6 • Supervising bodies' general comments

Le Président de l'Université Paris-Sud

à

Monsieur Pierre GLAUDES
Directeur de la section des unités de recherche
AERES
20, rue Vivienne
75002 Paris

Orsay, le 14 mai 2014

N/Réf. : 120/14/JB/LM/AL

Objet : Rapport d'évaluation d'unité de recherche
N° S2PUR150007982

Monsieur le Directeur,

Vous m'avez transmis le 3 avril dernier, le rapport d'évaluation de l'unité de recherche « Petites molécules de neuroprotection, neurorégénération et remyélinisation » - SMOREPAIR- N° S2PUR150007982, et je vous en remercie.

L'université se réjouit de l'appréciation portée par le Comité sur cette unité et prend bonne note de ses suggestions. Monsieur Michael Schumacher, directeur de l'unité, d'accord avec l'essentiel de ces appréciations, n'a pas souhaité faire remonter des observations générales.

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


Jacques BITTOUN
Président
Bâtiment 300
91405 ORSAY cedex