Neuroprotection et neurorégénération: molécules neuroactives de petite taille

Rapport Hcéres

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

Section des Unités de recherche

Evaluation report

Research unit

Neuroprotection and Neuroregeneration : neuroactive small molecules

University Paris 11

March 2009

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Section des Unités de recherche

Evaluation report

Research unit

Neuroprotection and Neuroregeneration : neuroactive small molecules

University Paris 11

Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

March 2009

Evaluation report

The research unit :

Name of the research unit : Neuroprotection et Neuroregeneration : neuroactive small molecules

Requested label : UMR_S INSERM

N° in case of renewal :

Head of the research unit : M. Michael SCHUMACHER

University or school :

University Paris 11

Other institutions and research organization :

INSERM

Date of the visit :

February 4th, 2009

Members of the visiting committee

Chairman of the commitee :

M. Yves AGID, Institut du Cerveau et de la Moelle épinière, Paris

Other committee members :

M. Cordian BEYER, Institut für Neuroanatomie, Aachen, Germany

M. Rainer RUPPRECHT, Max-Planck-Institut für Psychiatrie, München, Germany

Ms Roberta DIAZ BRINTON, University of Southern California, Los Angeles, USA

M. Maurice TANGUI, Université Montpellier 2, France

CNU, CoNRS, CSS INSERM, INRA, INRIA, IRD representatives :

M. William ROSTENE, CSS INSERM representative

No CNU representative was available on the day of the visit.

Observers

AERES scientific representative :

Ms Jocelyne CABOCHE

University or school representative :

M. Jacques BITTOUN, University Paris 11

M. Dominique EMILIE, University Paris 11

Research organization representatives :

Ms Catherine LABBE-JULLIE, INSERM

Ms Annick SALIN, INSERM

Evaluation report

1 • Short presentation of the research unit

- Number of members : 33 including
  - 4 researchers with teaching duties
  - 8 full time researchers
  - 5 PhD students, all with a fellowship: 2 MRT, 2 foundations, 1 private funding
  - 4 engineers
  - 12 technicians and administrative personnal
- Number of HDR : 7, 3 being PhD student advisor
- Number of PhD defended during the past 4 years : 6
- Average length of a PhD : 3.5 years
- Number of PEDR : 0
- Number of publishing lab members : 12 out of 12

2 • Preparation and execution of the visit

The review proceeded in several stages. First, the unit director gave an overview of the past and future activities of the laboratory. Second, several members of the three teams of research presented their research programs. Third, interviews were conducted with neuroscience faculty, students and engineers, technicians and administrative staff. Finally, the members of the Visiting Committee had an excellent discussion concerning the three teams and the entire laboratory.

This visit was remarkably organised, although the time allotted for the discussion was a little bit too short. However, due to the fact that the scientists of the laboratory are well known, and several members of the visiting Committee were experts in the field, an intensive review has been conducted.

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

Such a review is always difficult to provide, in particular to describe the areas of strength with regards to the scope of modern neuroscience and to identify areas of opportunity for future growth of the laboratory. Therefore, we did not attempt an exhaustive evaluation of each individual or each scientific sub-program.

From a general point of view, members of the Visiting Committee were impressed by the scientific presentations and the following discussions which enabled to provide a good qualitative evaluation. The favorable personal impression of the external review committee needs to be taken into account, keeping in mind that the standard means used to evaluate a laboratory of research – essentially based on the numbers of citations – might have lead to a relatively less satisfying evaluation for the laboratory. In particular, all the experts were impressed by the reputation of the laboratory at the international level (three of them indicating that this laboratory was the first in the world in this field). One needs probably to keep in mind the following : this laboratory has clearly modified its scientific strategy during the past years from the

study of steroids in the strict sense of the word towards neurosciences, i.e the role of various steroids, as neuroprotective agents, as actors of axons and mielyn repair, and as putative ligands to bind microtubules associated protein type 2 ; the remarkable capacity of the Director of the laboratory to ensure the cohesion and the coherence of the research activities ; the recent links established locally with various clinical departments, including neurology and anesthesiology (not neurosurgery at this time) ; the development of national and international scientific cooperations ; the quantity of the cooperations with industrial partners, as examplified by the implementation of a start-up (Mapreg). Moreover, in the large building of Inserm, providing enough lab space, several methods have been appropriately developed to reinforce the research programs. Finally, the Visiting Committee was impressed by the local excellent atmosphere.

This excellent qualitative impression is balanced by the quantitative assessment of the scientific articles, however, keeping in mind the high number of tenures in the laboratory (ex : 2006 : 9 papers in the field of biology, 10 clinically oriented papers ; 2007 : 11 in biological, 8 clinical articles). Papers with high impact factor are published mostly in PNAS or as reviews. Moreover the links between articles in the field of neurobiology and those published in the field of clinical research are not yet evident.

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

Team 1

The focus of Team 1 is investigation of the neuroprotective action of neurosteroids and regeneration of myelin. These studies include determining the mechanism of action that underlies neurosteroid-induced outcomes. Overall Team 1 has made remarkable progress in advancing the scientific understanding and translational therapeutic potential of neurosteroids in brain, particularly the neuroprotection induced by progesterone and its critical role in promoting myelination of axons within the central nervous system.

Two major advances have emerged from the research of Team 1. The first advance is the direct result of determining the neuroprotective effects of progesterone and the observation that the injured brain responds by synthesizing progesterone in vivo.

The second advance derives from analyses of the sites and mechanisms of progesterone action and particularly that progesterone is a potent and significant inducer of myelin synthesis in oligodendrocytes. Both discoveries form the foundation of clinical trials, one that is ongoing in the United States to determine the efficacy to reduce adverse effects of traumatic brain injury and the second clinical trial by Team 2 testing progesterone treatment of women with multiple sclerosis. Furthermore, the project presented proposed to further strengthen the mechanistic analyses of progesterone effects.

Methodological strengths include the GCMS resource for measuring steroids in brain and spinal cord developed by Team 1, the nerve injury mouse models and the availability of the PRA and PRB knockout animals. The development of a sensitive and reliable GCMS strategy for quantitatively measuring steroids in brain is a major achievement that no other laboratory has achieved for measuring steroids from the small sample volumes derived from rodent brain and plasma. Some concern was raised regarding the breadth of experimental animal models being pursued or developed.

A point of weakness for this Team is the low number of graduate students conducting research in this area. Leader of Team 1 has taken a very proactive and demanding approach, by taking on the additional responsibility of directing the Neuroscience Graduate Program.

Overall, Team 1 has been highly productive from both a basic science discovery and translational research perspective. Team 1 has secured extramural funding in addition to INSERM funding to support the costs of their research. Further, Team 1 has developed an internationally recognized standard for the precise detection and measurement of neurosteroid generation in brain. Proposed future studies build on this solid foundation to advance basic science discovery of neural effects and mechanisms of neurosteroid action in the nervous system. The outstanding caliber of the research, the productivity of the team, the basic science and translational significance of the research and proposed future investigations warrant further support at the highest level.

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 2

Team 2 presented four sub-projects concerning preclinical and clinical studies related to axon and myelin repair. This team represents the strongest team in the unit with translational clinical approaches which have been developed from long-lasting and seminal experimental studies. Composed of 4.5 full-time researchers, this team is in close relation with 4 clinical practitioner/investigators. The main orientation is axon and myelin regeneration in different pathological models such as motor neurons/peripheral neuron diseases, pain, and multiple sclerosis. These teams (projects) are strongly supported by industrial grants (i.e. Biotech Biocodex). This team is 50% co-headed by two researchers, and a senior researcher is supposed to complete the team for the next years coming from Pasteur Institute.

The scientific aims are to better understand the peripheral nerve regeneration after injury mainly focused on the use and understanding of the mechanism of action of Etifoxin, an anxiolytic drug that this group has found to be very potent to induced nerve regeneration. Etifoxin is a ligand of TSPO (translocator protein) known as the peripheral benzodiazepine receptor. This compound acting via TSPO not only induced axonal regeneration following injury such as freezing of sciatic nerve and increased myelinisation but also stimulated steroid synthesis. The team wants to develop a new orientation demonstrating that, via the steroid synthesis, Etifoxin can act on mitochondrial function and inflammation to induce nerve regeneration. Though until now experiments were carried out in vitro, they expect to use specific Cre-Lox mice in collaboration.

Around this main scientific orientation, two clinical groups were added in 2006 during the last evaluation of the unit. The period of this cooperative pre-clinical and clinical approach is too short to provide significant and published results of this translational work but shows promising data in cooperation Department of Neurology and Anesthesiology of Bicêtre hospital. For example, the Neurology group is studying an experimental paclitaxel-induced neuropathy used for cancer treatment in humans. The Department of Anesthesiology is investigating neuropathic pain induced by inflammation and, additionally, contributes classical behavioral tests for neuropathic pain which were developed in an external laboratory in Bicêtre.

Besides the role of Etifoxin on nerve regeneration and pain concentrating, team 2 expedites two further clinical research projects. A multicenter PHRC on neurosteroids and cognition in humans associated with Alzheimer´s disease. The aim of the first project is to correlate human plasma levels of pregnenolone sulphate as measured with a highly sensitive mass spectroscopy methodology developed in the lab (GC-MS) with memory deficits observed in Alzheimer´s patients. The second projec is an EU clinical trial on progesterone and estrogen substitution in multiple sclerosis patients in France with the hospices civils de Lyon. The aim of this project is to substantiate preclinical studies which have been demonstrated as curative therapeutic strategy for relapsing remitting multiple sclerosis. Relapse rates are monitored by neurological and neuro-imaging (MRI) techniques (in collaboration with with LIMEC in Bicêtre) during 3 months following delivery under THS treatment.

Strengths :

- Substantial original experimental work done on the effect of steroids/neurosteroids on peripheral nerve regeneration including the related cellular mechanisms

- Good publication report per scientist in the past years in medium-good ranked journals

- The development of Etifoxin as a potential new therapeutic neuro-regenerative drug for the treatment for peripheral neuron disorders associated with demyelination

- Novel strategy to use neurosteroids as prognostication markers of neuropathological disorders (AD)

- Good concurrence between basic and clinical scientists and potential of future translational expertise

- Highly embedded into the important world wide scientific networks and labs related to neurosteroids and brain function and protection

- Perfect structure for further industrial funding

Weaknesses :

- Running the risk of following too many orientations with a limited number of senior scientists and dissipating the energy of the team (preferably focusing on the most promising clinical projects)

- Missing of a general superior clinical director of studies for better coordination of projects

- Better integration of PhDs and MDs in the projects (this is a general weakness of this INSERM unit)

- Need for more top quality publication (> 10 IP) in high standard journals

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	B	A	A	A

Team 3

Team 3 is dedicating its work to longevity and aging with special emphasis on neurosteroids. A major rationale for the work of this team is the discovery that pregnenolone binds to microtubule associated protein type 2 (MAP2) and that pregnenolone may have neuroprotective and memory enhancing properties. Three project lines are followed up by team 3. Project 1 is investigating the role of microtubular modifications for neurodegenerative diseases, project 2 is dealing with longevity and neurosteroids in C. elegans and project 3 tries to link these issues to depression. While project 1 and 2 are quite closely linked to the thematics of the other teams (neuroprotection), project 3 opens the psychiatric field, which so far has no further support by the other research group. Each of the projects is highly innovative and attractive on its own. While the projects 1 and 2 could be matter of translation in to clinical research as already initiated by the other teams, this appears to be more difficult for project 3. The link to the MAPREG company has been delineated as a mutual benefit, since MAPREG also supports the INSERM research by providing funding. One structural issue is that the leadership of team 3 totally depends on the team leader. Therefore, the recruitment of a senior researcher, who could take over also management responsibilities, might be an option. However, according to discussions with the unit director, this team could merge with team 1 or 2.

The primary focus of this team is to investigate neurosteroid binding to and modification of microtubules which is a highly novel area of research and is unique to this research team. This discovery promises to be a significant advance to the understanding of neurosteroid action in neurons in particular and of steroid regulation in fundamental cell biology. The potential basic and translational science advances from this project are substantial and deserve continued support.

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	B	A+	B	A

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

Researchers :

Among the 7 researchers with permanent position, one is from Morocco, one is from the UK and the others are French. They have but considered not enough technical help (which seems to be usual in Inserm teams). Authorship is considered as fair. The researchers actively participate in grant writing. Money is a problem, since there is not enough university budget for all their projects. There is a formal lab meeting which is intended once a month, moreover, there is a journal club. The researchers are not obliged to teach, but most of them do on a voluntary basis. One MD is working half time in clinical anesthesiology, half time in basic research. Another MD is doing 10% clinical work.

Engineers, technicians and administrative staff :

The committee could discuss directly with the 14 technicians, engineers and administrative staff members present. They express their global satisfaction regarding the working conditions in the laboratory, in terms of involvement in the collective tasks, participation to the lab committees, recognition through the scientific production, access to professional training and listening by the researchers of lab director. Despite a limited proportion of non-permanents, a general worry on career advancement has been outlined. One technician recruited in 2005, several retirements to be expected in the following years.

6 • Recommendations and advice

— Strong points :

In this field of research this laboratory seems to be a leading one at the international level.

The director of the laboratory has been able to ensure the coordination of the different research activities, a challenge which is not obvious in the presence of the emblematic famous professor…

Taking into consideration the past history of this laboratory, there are real potential discoveries to be made.

Efforts of the experienced investigators to implement national and international scientific collaborations.

Initiation of cooperations with industrial partners, including the presence of Mapreg, a start-up which is almost part of the laboratory.

Initiatives to open the scientific activities towards clinical practice.

Development of numerous methological approaches including GCMS resources for measuring steroids in brain and spinal cord.

Excellent laboratory facilities and excellent atmosphere within the lab.

— Weak points :

The level of publications, as estimated by number and the ratio impact factor (and H factor) on the number of tenure researchers and technicians, is insufficient.

Aging of several of the tenures contrasting with the relatively low number of students including post-docs, PhD and Masters.

Surprising number of experimental models with a risk of taking the drugs used, not as tool for research but for the purpose of the industrial partners.

Risk for the future to develop too many scientific research programs.

There is a need for the laboratory to find a clinical coordinator in order to facilitate the starting synergy between the clinical approaches and the traditional activities of the laboratory.

— Recommandations :

The most important : to focus the efforts of the different teams on selected scientific projects : pregnenolone and Map2; myeline repair ; trophic activities of progesterone.

There is a need to increase the number of rank A articles and top publications in high general standard journals.

An effort has to be made to hire young and brilliant scientists to ensure the future of the laboratory (in particular post-docs).

Nevertheless, it is crucial to perpetuate the characteristics of this laboratory, i.e. to take advantage of the results of basic research to target new drugs for the repair of the injured nervous system.

Although several efforts have been done in this area, the advice would be to ask for large grants at ANR, European Community, Human Frontiers, etc...

In conclusion, this visit was really of interest as it showed that the standard means formerly used to evaluate a laboratory of research – essentially based on the number of citations… - would lead to a good but relatively modest evaluation of this laboratory. The discussions with the different investigators, following brilliant, although too short presentations, enable the members of the Visiting Committee to provide a qualitative evaluation which is more appropriate. This very likely explains the difference between the personal impression of the external Review Committee and that of the standard assessment forms.

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	B	A	A	A

Inserm

Institut national
de la santé et de la recherche médicale

UNIVERSITÉ PARIS-SUD 11

UMR 788
Steroids, neuroprotection and neuroregeneration
Director : Michael Schumacher

GENERAL OBSERVATIONS ON THE REPORT FROM THE VISITING COMMITTEE

New title of the Research Unit :

Neuroprotection and neuroregeneration : neuroactive small molecules

Inserm and University Paris-Sud 11

Reference* : *EVAL-0911101C-S2100012389-UR-RPRELIM

We wish to thank the Chairman and the members of the Visiting Committee for the very positive and valuable assessment of our research unit, and in particular for their strong support for our translational research projects. We are also grateful for their recommendations and advice, which encourage us to pursue our efforts to bridge the divide between basic biomedical and clinical research, to foster collaborations with pharmaceutical and start-up companies, and to further strengthen our research performance. We consider the recommendations of the Committee as very constructive for our efforts to sustain our dynamics of improvement, and we wish to take the opportunity to reply to some specific points.

Although the Committee considered our laboratory as highly productive from both a basic science discovery and translational research perspective and recognized our great reputation at the international level, the quantitative assessment of our publications (numbers of citations) was considered as less satisfying with regard to the number of tenure researchers and technicians in our unit. The Committee expressed a need for more top quality publications (> 10 IP) in high standard journals.

It is indeed one of our objectives for the next four years to publish more in very high impact factor journals, and we are setting up the tools necessary to achieve this goal. In fact, our biomedically-oriented *in vivo* research often meets difficulties in elucidating cellular and molecular mechanisms with available pharmacological tools, preventing us sometimes from publishing original and relevant findings in very high impact factor journals. A first solution to this problem will be the use of the Cre-lox technology, allowing the inactivation of genes within specific tissues or cell types. An example allows the power of this approach to be illustrated. Thus, we have recently demonstrated the remarkable beneficial effects of etifoxine on axon elongation and neuroinflammatory response after peripheral nerve injury, and these experimental observations form the basis for a future clinical trial to be conducted in the Department of Neurology of the Bicêtre Hospital. However, existing pharmacological inhibitors do not allow us, for the moment, to specify the roles of the mitochondrial translocator protein (TSPO) and of neurosteroids in the beneficial actions of etifoxine. This will now be achieved by selectively inactivating either the expression of TSPO, or of a key enzyme involved in neurosteroid biosynthesis, or of the progesterone receptors in the nervous system, and more specifically in neurons and glial cells. A second strategy is the use of the zebra fish model, which has become a leading model organism thanks to its superb transparency and easy genetic manipulations, and because critical molecular

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mechanisms involved in processes such as axon elongation and myelination are conserved in fish and in other vertebrates. We are confident that these strategies will give us access to journals such as *Nature* and *Science*.

On the other hand, we think that it is important to continue publishing in *high quality* specialized journals. Leading journals in a specific field are indeed not only the ones with very high impact factors, and impact factors for leading specialized journals are in general between 4 and 8. For example, we continue publishing breakthroughs and novel analytical methods for the analysis of steroids by mass spectrometry in the *Journal of Lipid Reseach*, which is a leading journal in the field of lipid biochemistry, but with the modest impact factor of 4.3. In the fields of endocrinology and pain research, the journals *Endocrinology* and *Pain* are leading ones, but with impact factors around 5. Most importantly, clinically relevant biomedical research is generally published in journals with relatively modest impact factors. Thus, two of our preclinical studies conducted in collaboration with industrial partners have been published in the *Journal of Pharmacology and Experimental Therapeutics* (IF = 4), which is a reference in the field. One of the molecules tested within the frame of these studies has now reached Phase 2 trials. However, we wish to attract the attention that we already publish in very high impact factor journals, and we have recently contributed to a second article in the prestigious *New England Journal of Medicine* (the highest impact factor of 52.5), accepted for publication in March of this year, after the examination of our unit by the Committee.

The "h Index" has become another factor for evaluating the scientific productivity and scientific impact of researchers. Interestingly, this index is not based on journal impact factors, but on the citations received by publications, and thus more accurately reflects the impact of the work of a researcher within the scientific community. In this context, it is important to note that the "h Index" of the Director of UMR 788 is 28, which ranks him among the World's leading scientists in the field (calculation by Scopus in December 2008, offered by the courtesy of Elsevier). Other researchers of our laboratory also have a significant h Index, thus reflecting the reputation of our laboratory at the international level. Of course, not all tenure researchers of our laboratory publish at the same level, but this can be explained by other commitments and responsibilities : the MCU has heavy teaching duties (192 hours/year), one senior scientist is responsible for a hospital-based multicenter clinical research program (PHRC), another senior scientist is involved in a clinical trial (POPART'MUS) and the PU-PH and PH have time consuming clinical activities. Thus, the 4 researchers with teaching duties only correspond to 1.8 full-time equivalents (FTE) for our laboratory, and the 8 "full time" researchers correspond in fact to 7.4 FTE.

In our report of activity, we had listed the scientific production of our research unit among the "strong points" : 123 publications since 2004 (95 papers in the field of biology and 28 clinically oriented papers) ; 35 articles with an Impact Factor > 5 ; 49 articles with an Impact Factor > 4.

Highlights :

1 New England Journal of Medicine	IF = 52,6 (a second article accepted in March 2009)
1 Lancet Neurol	IF = 10
1 Brain	IF = 8.5
4 Proc Natl Acad Sci USA	IF = 9.6
2 FASEB J	IF = 6.8
4 Neurology	IF = 6.0
1 Aging Cell	IF = 5.8
2 Molecular Endocrinol	IF = 5.3
5 Endocrinology	IF = 5.1

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Some international high-impact reviews :

Endocrine Reviews	IF = 18.5
Prog Neurobiol	IF = 10.5
Pharmacol Ther	IF = 7.9
Brain Res Rev	IF = 6.5
Curr Opin Pharm	IF = 6.4

We also wish to stress that part of our review articles, published in prestigious international journals, propose novel conceptual frameworks and thus significantly contribute to the international reputation of our laboratory.

The Committee has raised concerns regarding the number of experimental models and the risk for the future to develop too many scientific research programs with a limited number of senior scientists.

We agree with the Committee that it will be important not to dissipate our energy and to focus more on major problems during the next four year period. Over the past four years, we have indeed investigated the role of steroids and TSPO ligands in a variety of models of neuroprotection and neuroregeneration, but this can be explained by the fact that our laboratory was in a phase of exploration. As acknowledged by the Committee, we have indeed recently extended the study of steroids from their classical functions towards their roles in regulating neuronal and glial plasticity, neuroprotection, regeneration and myelination. By chance, our research efforts have allowed important roles of steroids in the different models to be documented, and they have revealed the significance and pleiotropic nature of steroid actions in the nervous system. We now intend to focus our efforts on some of the major trophic and protective effects of steroids, as for example their roles in axonal regeneration, microtubule dynamics and myelin formation, and to go further into their mechanisms of action. However, our wish to focus our efforts on a limited number of problems also has to take practical realities into account : the need for financial support from different sources and the need for researchers and clinicians to develop their own research projects within the frame their professional careers.

It is also important not to limit our investigations to specific steroids such as progesterone or pregnenolone, as within an organism and under specific physiopathological conditions, different hormones always act in concert, sometimes mutually reinforcing their effects, but sometimes also exerting inhibitory actions. To strengthen the clinical perspectives of our work, it was also necessary to extend our investigations to other small neuroactive molecules, with molecular weights in the range of 300 Daltons, such as TSPO and immunophilin ligands and local anesthetics. The two former indeed play important roles in the synthesis and actions of steroids within nervous tissues, and the latter could provide strong protection against side-effects such as chronic pain, which may result from the strong stimulation of regenerative processes.

The Committee also mentioned the risk of testing molecules not as a tool for research, but only for the purpose of industrial partners.

We have to be realistic about the constraints imposed by collaborations with industrial partners, as they invest money to answer very specific questions. In the case of routine investigations for pharmaceutical and start-up companies, it is possible to invoice services allowing the financing of additional fundamental research. Nevertheless, companies are also often interested in elucidating the mechanisms of action of their molecules, in fundamental problems and in opening new avenues. An additional strategy we adopted is to use the molecules we test within the frame of

specific contracts as pilot molecules for our research problems. For example, the compound etifoxine we are studying for Biocodex Company, offers an exceptionally interesting and powerful tool for investigating both *in vivo* and *in vitro* new fundamental mechanisms and principles involved in neuroprotection and neuroregeneration.

It is important to note that all our contracts with private companies are managed by Inserm-Transfert and approved by the "Service of Industrial and Commercial Activities" (SAIC) of University Paris-Sud 11.

The Committee has also addressed the aging of several of the tenure researchers and recommended efforts to be made to hire young and brilliant scientists to ensure the future of the laboratory (in particular post-docs).

This is indeed a major challenge for our laboratory, like for many research units within the context of the rapidly aging population of researchers in our country, in part because of the extremely unfavorable age pyramid of tenure scientists, teaching and technical staff. We are making important efforts to renew the research potential of our laboratory :

1) There are 5 postdoctoral fellows in our research unit, and some of them may succeed in obtaining a tenure position. Team 1 has been strengthened by the arrival of Marcel Tawk, who last year obtained a prestigious Junior Fellowship from Inserm, and who is starting to apply for a position of "Chargé de Recherches". He has recently published an article in *Nature*. An excellent postdoctoral fellow of team 2, Christelle Girard, who has just published an article in PNAS, will apply for a MCU position at our University. Another brilliant and promising postdoctoral fellow, Massimiliano Bianchi, has joined team 3. Thus, there is hope for more young tenure scientists.
2) Liu Song, a young "Chargé de Recherches Inserm" now working at the Pasteur Institute, will join team 2 in January 2010.
3) Negotiations are in progress with another research team, which may join our unit in the very near future.

The separate evaluations of the 3 research teams.

We are glad that the Committee has very positively evaluated each one of the 3 research teams, and has acknowledged their specific roles and values. For all the teams, we consent that research efforts have to be focused during the next four years, as already discussed above for the general research strategies of our laboratory. We will also make efforts to increase the number of PhD students (at this time 5 PhD students). The teaching activities of members of the laboratory, and the fact that the Director of the laboratory will take next year the additional responsibility of a doctoral school of University Paris-Sud 11, will result in a stronger involvement of our research unit in the training of PhD students.

The Committee particularly appreciated the translational clinical approaches of Team 2, but has recommended a better coordination of the projects by a general superior clinical director of studies. Professor David Adams (PU-PH) of the Department of Neurology is co-responsible with the Director of the research unit for team 2, which also includes members of the Departments of Anaesthesia and Intensive Care and of Neuroradiology, thus federating the forces in neurosciences of our campus. We are confident that the collaborations with the clinicians will become very successful and productive because of the complementary expertise and because of excellent relationships. The Committee had indeed noted the good atmosphere in our unit. The close collaboration with the Department of Neurology and Biocodex Company allowed combined publication in December 2008 in PNAS of observations on the exceptional effects of the TSPO

ligand etifoxine on peripheral nerve regeneration, results which will provide the basis for a clinical trial in our Hospital. The expertise of the Department of Anaesthesia and Intensive Care now allows us to also include the very important aspect of chronic neuropathic and inflammatory pain in our studies aimed to promote regenerative processes in the nervous system. A joint grant application was submitted to AFM last month. After some initial difficulties due to technical limitations, the collaboration with the Department of Neuroradiology is also becoming very promising, and we have been recently successful in applying Diffusion Tensor Magnetic Resonance Imaging (DT-MRI) technology for the tracking of nerve fibers in the rat spinal cord.

The Committee has also appreciated the three highly innovative research projects of team 3, and the direct link of the team to MAPREG company, which provides significant funding for Inserm research. This start-up has indeed emerged from our research unit and remains closely associated. We also wish to attract attention to a very important recent finding of the team, the direct interaction of the immunophilin FKBP52 with TAU microtubule-associated proteins, which opens completely new perspectives for the understanding of neurodegenerative diseases such as Alzheimer's disease. The Committee expressed some concerns about project 3 of team 3, which is about the significance of steroid effects on microtubule dynamics for depressive and anxiety disorders. However, we feel that this project is well integrated within the general program of our research unit, as its focus is on a novel aspect these psychiatric disorder, closely linked to our problematics of neuroprotection and neuroregeneration. Finally, the Committee also raised a structural issue, as the leadership of team 3 depends on the "emblematic famous professor". In the opinion of the Director of the laboratory, this is not a problem for next four-year period, as the Professor responsible of team 3 enjoys excellent health and is very dynamic and creative. It is an exceptional situation that Etienne-Emile Baulieu and Michael Schumacher not only manage to live side by side, but also continue to collaborate and to have excellent relations. This remarkable harmony, unfortunately unusual in the scientific community, is of great benefit for the research projects of our unit and for Inserm. However, to preserve the well-balanced functioning of our laboratory, it is essential that Etienne-Emile Baulieu keeps his own team. In a more distant future, if the famous Professor intends to invest his energy into other projects, members of team 3 may be smoothly integrated into the other teams thanks the complementarity of the research projects. But this is not an issue for the moment.

Kremlin-Bicêtre, April 9, 2009

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