BMNTS - Biopathologie de la myéline, neuroprotection et stratégies thérapeutiques

Rapport Hcéres

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

Research Units Department

AERES report on unit:

Biopathology of Myelin, Neuroprotection and Therapeutic Strategies
BMNTS

Under the supervision of the following institutions and research bodies:

INSERM
University of 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:	Biopathology of Myelin, Neuroprotection and Therapeutic Strategies
Acronym of unit:	BMNTS
Label requested:	UMR Mono-Organisme INSERM
Present no.:	EA 4438, UMR 7237 (CNRS) and partly U666 (INSERM)
Name of Director (2009-2012):	
Name of project leader (2013-2017):	Mr Guy MENSAH-NYAGAN

Members of the committee of experts

Chair:	Ms Anne BARON-VAN EVERCOOREN, Paris
Experts:	Ms Nathalie CARTIER, Paris
	Mr Luis GARCIA-SEGURA, Madrid, Spain
	Mr Jérôme HONNORAT, Lyon (CSS INSERM representative)
	Ms Rebecca MATSAS, Athens, Greece
	Mr Michael SCHUMACHER, Kremlin-Bicêtre
	Mr Denis VIVIEN, Caen (CNU representative)

Representatives present during the visit

Scientific Delegate representing AERES:

Mr Christian GIAUME

Representatives of the unit's supervising institutions and bodies:

Ms Catherine LABBE-JULLIE, INSERM

Mr Eric WESTHOF, University of Strasbourg

Report

1 • Introduction

Date and conduct of visit: 23/02/2012

The visit started at 9 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 "Biology of Myelin Diseases and Therapeutic Strategies: animal models and myelin repair" and, later, the researcher in charge of the theme "Mechanisms of Neuronal Protection in Myelin Pathologies », followed by a short presentation by a young post-doc researcher on "Behavioral and Neurochemical Evidence for a Neuroprotective Role of Neurosteroids against Anticancer Drug-induced Peripheral Neuropathies". After lunch, the committee members and the AERES representative had a closed-door meeting with the supporting organizations representatives (University of Strasbourg, Faculty of Medicine and INSERM). This was followed by a presentation by a young post-doc researcher on "Involvement of Nuclear Receptors of Vitamin D and Retinoids in Myelin Repair". Finally, the committee members listened and questioned the researcher in charge of the theme "Clinical Aspects of Myelin Disorder Therapies".

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.

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

This project "Biopathology of Myelin, Neuroprotection and Therapeutic Strategies, BMNTS" will reunite two research teams: "Steroids, Neuromodulators and Neuropathologies, EA-4438 and "Biopathology and Imaging of Myelin, LINC, UMR 7237 CNRS /University of Strasbourg and will incorporate 3 faculty members currently located at INSERM Unit 666 (Animal models of synaptic disconnection: morphological markers). They are all located at the Faculty of Medicine since 2009. They will gather in a single research structure for the period of 2013-2017.

Management team:

Mr Guy MENSAH-NYAGAN has an unquestioned international visibility in the field of steroids, neuromodulators and neuropathologies. He will be the director of the Unit for the next five years. The unit's project will be a single theme Unit with different research axes centered on (i) biopathologies of myelin, (ii) neuroprotection and (iii) therapeutic strategies.

Unit workforce:

Workforce	Number on 06/30/2011	Number on 01/01/2013	2013-2017 Number of producers**
N1: Professors or assistant professors	7	7	7
N2: EPST or EPIC researchers	3	3	3
N3: Other professors and researchers	3	3	3
N4: Engineers, technicians and administrative staff *on a permanent position	4.5	4.5	
N5: Engineers, technicians and administrative staff * on a non-permanent position	1		
N6: Postdoctoral students having spent at least 12 months in the unit	3		
N7: Doctoral students	7		
N8: PhD defended	9		
N9: Number of Habilitations to Direct Research (HDR) defended	1		
N10: People habilitated to direct research or similar	8	8	
TOTAL N1 to N7	**28.5**	**17.5**	**13**

* **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 an excellent project relying on the complementary expertise of 3 groups which have separate histories but common interest in myelin repair and neuroprotection. The members of the proposed unit are active and productive scientists who have significantly contributed to the field of myelin biology, myelin pathology and neuroprotection. The research activity of the proposed unit is devoted to translational research, their interest being to identify new promising targets for the development of therapeutic strategies effective against myelin diseases, such as painful peripheral neuropathy, remyelination and neuromyelitis optica. The project is focused on multidisciplinary and translational approaches and is based on unique experimental animal models of myelin pathologies and efficient therapeutic strategies for the treatment of myelin deficiency and axonal damage.

Strengths and opportunities:

Three existing teams will reunite around a common theme addressing “myelin repair and neuroprotection” for myelin diseases under the supervision of a very good leader with strong visibility and recognition, and high motivations. They benefit from a very good local, national and international integration with a strong support of the local hospital and university. The committee has appreciated the multidisciplinary approach, the excellent interaction between clinical and basic research, the originality of the approach based on the morphological examination to guide more molecular investigations. The project has strong support of the University and enters in the axes of research considered as priorities in biomedical research in Strasbourg, comprising the University, the Federation of translational medicine and the CHU.

Weaknesses and risks:

As a whole the scientific project is very wide and needs to be more focused. A major concern is the many experimental models and subprojects proposed, and the many potential therapeutic agents to be evaluated, which appear not compatible with the small size of the future team. Also, not all of the proposed subprojects are of equal quality.

Moreover 3 full time researchers will have to be replaced during the course of the new project, and about 60% of the personnel is over 55 years of age pointing to the urgency to recruit young investigators.

There is a limitation in PhD students due to a limited number of HDR (5).

Recommendations:

Based on the documents provided and the oral presentations performed, the committee members would like to make the following recommendations to the principal investigator and his team members, in order to help them to identify, among the large number of projects presented, which ones are the more promising and original to focus their research program. All the committee members found the projects presented of interest, with clear multidisciplinary approaches and for some of the projects presented a good chance of translation to clinic. The complementary of the team members, including people with background on pharmacology, biochemistry, molecular and cell biology, physiology and behavior in addition of a strong expertise in anatomo-pathology, in neurology and in the design of clinical trials, should be used to provide a stronger added value to a more limited number of well identified projects. This does not mean that the other projects are not of interest, but that they should be considered, at the present time, as emerging. Accordingly, these recommendations should be considered by the team leader and his co-workers as positive signs demonstrating the interest of the committee members for the proposed application.

The committee of experts has invited the team leader to clearly define priorities. It is strongly recommended to the project leader to focus efforts on a limited number of subprojects and to reduce the number of experimental disease models and of therapeutic molecules to be investigated.

3 • Detailed assessments

Assessment of scientific quality and production:

Three previous research teams propose to join their efforts by proposing the creation of a new single-team research unit entitled "Biopathology of myelin, neuroprotection and therapeutic strategies" (BMNTS). Each of the founding teams has carried out original and important work over the past 5 years, with significant impact in the scientific community. The heads of the previous research teams will be responsible of specific research projects within the new unit.

The leader of the present project headed the part of the project entitled: "Steroids, neuromodulators and neuropathologies". He has an international reputation in the field, testified by his publications in international high quality journals (16 original articles and 10 reviews over the past 5 years) and his participation in international meetings: 20 invited lectures and 5 meetings organized by himself. As a full professor, he has also a very strong commitment to teaching and education. A major achievement of the team was the discovery that an increase in the synthesis of specific neurosteroids, in particular of the progesterone metabolite allopregnanolone (3α,5α-THP) and estradiol, is part of endogenous neuroprotective and analgesic responses. This concept has opened the way for the therapeutic use of neurosteroid compounds and has led to a recent patent application related to the use of neurosteroids as drugs for the preventive and curative treatment of neural diseases (BRE1). Investigations concerning the interactions between gamma-hydroxybutyrate (GBH) and neurosteroids have opened a new and original line of investigation, which already resulted in a second patent application related to the use of GHB as brain metalloproteinase inducer for the treatment of neurodegenerative diseases (BRE2).

The responsible of the part of the project entitled: "Biopathology and myelin imaging" is an internationally recognized expert in myelin biology and imaging technologies, in particular diffusion tensor MRI (DTI). Since 2006, he has co-authored 12 original publications in high quality journals, including 3 in the Journal of Neuroscience. His expertise in regenerative processes and recent interest in hormonal influences on myelin repair (thyroid hormones and androgens) justifies to join the new research unit. At the experimental research level, major internationally recognized achievements were: (1) the demonstration that specific DTI parameters can be used to evaluate myelin damage and repair; (2) the establishment of very valuable models of reversible or irreversible demyelination (Oligo-TTK mice); (3) the observation that the structure of myelin sheaths differs between males and females; (4) the finding that androgens and thyroid hormones can stimulate the remyelination of axons, even in chronic demyelinating lesions where no spontaneous myelin repair takes place. These findings have led to a clinical trial aimed to test the therapeutic usefulness of the T3 analogue Levothyrox in multiple sclerosis (MS) patients and to a patent on the therapeutic use of androgens in demyelinating diseases. This part of the team has also contributed to progress in MRI imaging of myelin by developing new contrast molecules. Other important results were the correction of myelin disease phenotypes by siRNA strategies and the discovery that the palmitoylation of myelin proteins increases their immunogenicity, with consequences for autoimmune myelin diseases; the latter discovery has led to the generation of a new experimental model for Guillain-Barre syndrome and the successful testing of lipopeptides in experimental models of MS (patent application). A particular strength of this team is the close association between basic researchers and clinicians. The neurologists of the team are leaders in MS and in neuroinflammatory diseases such as "neuromyelitis optica" (NMO), as it is testified by their large number of publications (55 original articles co-authored) and participation in clinical MS trials.

Finally, the last part of the project entitled: "Animal models of synaptic dysconnection: morphological markers" was headed by a senior who has 16 original publications in international journals over the past 5 years. Her research interest has been the morphological characterization of two animal dysconnection models for schizophrenia: the "Stable Tubulin-Only Protein" (STOP) mouse and rat ventral hippocampal lesion. This team will thus strengthen the new unit with its competence in neuromorphology and has already collaborated with other members of the team. Expertise in transgenic models is provided thanks to the recently recruited MCUPH trained at IGBMC, who appeared as first author on 9 original publications over the past 5 years in high-impact factor journals. In particular, mouse lines carrying null mutations of nuclear receptors for steroids, retinoic acid and thyroid hormones and conditional knockouts and generated at IGBMC, will be valuable for the projects of the new unit.

In conclusion, the 3 founder teams of the new research unit are internationally recognized and have been very productive over the past 5 years in terms of publications (121 original articles published in high quality international journals such as Arch. Neurol., Brain Res. Rev., Cell. Mol. Life Sci., EMBO J., FASEB J., Genes Dev., Glia, J. Immunology, J. Neuroscience, Neurology, New England Journal of Medicine, Pain, PNAS and Progress in Neurobiology; 33% of publications in journals with IF>5; and 16 review articles, patents 5 applications), development of new concepts, generation of new disease models and clinical trials. All members publish on a regular basis. This is remarkable, as they are also strongly involved in teaching and pedagogic activities.

Assessment of the unit's integration into its environment:

The research activity of the proposed unit is devoted to translational research. Their efforts will be directly involved in finding solutions to socio-economic issues generated by myelin disorders, such as multiple sclerosis, neuromyelitis optica and peripheral neuropathy. This will be possible through one the team's PI, heading the Clinical Investigation Center (CIC) of the CHU.

Moreover, the leader of the team as full professor has very close links to the University through teaching and involvement of the personnel at the Master level.

Finally, several members of the team have international collaborations within Europe and USA, i.e through the NEUREX program they are involved in an ongoing collaboration between France, Switzerland and Germany.

They have a well-elaborated plan for technology transfer (by means of Servalor, Technology Transfer Service of the University of Strasbourg). In this respect they have filed 5 patents over the last 5 years.

Finally, dissemination activities are performed through multiple ways: teaching activities, supervision of PhD and master students (8), engineers and technicians (5), scientific publications and the plan to create an interactive website (prospective). Members disseminate their research results by various means: TV shows, public conferences, industry meetings and wide audience publications.

As far as external financing activities and participation in the activities of innovation clusters, members participate in several regional and European networks (NOMADMUS, FREEDOMS, ALSACEP, OFSEP, EDEN). Globally, members have been successful in obtaining external funding (365K€/2009 and 387.5k€/2010) from industry, ANR, Swiss National Science Foundation in addition to salaries (675K€/2009 and 673k€/2010).

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

The team leader is internationally recognized in the field of Neurosteroïds and is frequently invited to deliver lectures in international meetings and conferences in prestigious scientific institutions. He has participated in the organization of 5 international meetings. Predictions are that his recognition will be expanding over the years.

Another member of the team is an internationally recognized neurologist. He has become Director of the Clinical Investigation Center (CIC) of Strasbourg and conducts clinical biomedical research on neuromyelitis and multiple sclerosis patients at the national and international level. Finally, several members have also participated in many international scientific committees and in the organization of international conferences. They are involved in several European networks and maintain active collaborations with numerous foreign laboratories in Argentina, Australia, Canada, USA and Europe.

As far as their capacity to recruit researchers, post-docs and high-levels students, the team belongs to the ERASMUS Program, attracting students from Germany and Switzerland, and belongs to several masters (Neurosci, Biotechnology), Bachelor's degree (Health and Engineering), BTS in biotechnology. Moreover, the team leader is President/member of several boards related to teaching or scientific expertise. Several members are chairpersons of various teaching units (Semiology, Biochemistry, Hematology, Animal Physiology). The group has been able to attract last year a young MCU trained at IGBMC with an excellent curriculum vitae and a strong expertise in transgenic models. Of the actual 4 PhD students, two are part of a "co-tutelle" program respectively with a laboratory in Germany and in Switzerland.

Assessment of the unit's governance and life:

The head of the unit is highly motivated by the idea to pull together these 3 groups which have separate histories but common interests in myelin and neuroprotection. His initiative is excellent. He will take care of the coordination of the scientific activity by frequent general meetings but also sub-groups meetings, with team leaders and principal investigators. From an administrative point of view, he will have an internal council advising him on important scientific and administrative decisions to be made. His administrative task will be greatly helped by an administrator and account manager, both of them need to be recruited, with the help of the Dean of the Faculty of Medicine.

The proposed unit has an enormous strength. It will integrate basic scientists and clinicians with complementary and multidisciplinary expertise in neurology, histopathology, clinical biochemistry, behavioral analysis, in vivo imaging, electrophysiology, molecular biology and biochemistry, cell cultures, electron and confocal microscopy, immunochemistry and peptide synthesis. These basic scientists and clinicians plan to work in coordination in one or more of the 3 project themes. Scientific priorities must now be identified and reunions between PIs and students must be launched.

In-house communication will be encouraged through seminars, meetings and other common activities. Unit members will also be involved in laboratory training for students, technicians and researchers. Members of teams will have the opportunity to enroll in specific training programs.

Assessment of the strategy and 5-year project:

The project will be focused on multidisciplinary and translational approaches for the generation of experimental animal models of myelin pathologies and development efficient therapeutic strategies for the treatment of myelin deficiency and axonal damage. Their major goal is the identification of novel promising targets to develop therapeutic strategies effective for neuroprotection and remyelination, including painful peripheral neuropathy, multiple sclerosis and neuromyelitis optica.

A strong aspect of the research project is to focus on both myelin repair and neuron viability. This is important because of the reciprocal interactions between neurons and oligodendrocytes. This project is of high relevance for myelin diseases since myelin loss or anomalies are the cause neurological and cognitive alterations, and increase axon vulnerability to inflammation. The proposed translational program is highly relevant and straightforward, involving a multidisciplinary approach and close collaboration between researchers and clinicians, aimed at contributing to the development of new treatments for myelin pathologies. The project is based on the expertise, solid experimental ground and experimental models developed over the past 5 years by the members of the new unit.

The necessary scientific, medical and technological expertise and equipments for successful completion of the proposed project are available. A particular asset of the new team is its strong link with clinicians, the capacity to analyze experimental outcomes at the morphological and functional levels. For some projects, a more mechanistic approach should be considered, at both molecular and cellular level.

The following models appear particularly promising to the experts of the committee: (1) chemotherapy-evoked peripheral neuropathies, which are a major concern for cancer patients and allow preventive treatment with neuroprotective agents; (2) demyelination/remyelination (myelin repair) in relation to demyelinating diseases such as multiple sclerosis (MS); (3) neuromyelitis optica (NMO). Studies of MS and NMO models will indeed strengthen the link with the clinicians. In this regard, a particular asset of the new team is the appointment of one of its members in 2011 as director of the Clinical Investigation Center (CIC) of Strasbourg. He and his colleagues are conducting a high-level clinical biomedical research on NMO patients as part of a national project (NOMADMUS) and on MS patients as part of an international program (FREEDOMS). A new animal NMO model with translational readouts is needed.

Among the therapeutic agents (pharmacological tools) proposed to be studied, appeared particularly promising the synthetic analogues of allopregnanolone, already tested in psychiatric conditions such a premenstrual disorders, and provided by Umea Neurosteroid Center in Sweden. Synthetic androgens and thyromimetics also offer interesting therapeutic promises for myelin repair.

A more limited number of models would allow to go further into disease mechanisms. The recent recruitment of a young MCUPH, trained at IGBMC with expertise in transgenic models, should allow to investigate the role of nuclear receptors and coactivators in physiopathological signaling mechanisms.

Allocation of funds should be more clearly outlined.

The strengths of the project are:

- A very good leader with strong visibility, recognition and high motivations

- A high quality and frequency of publications

- A very good local, national and international integration with support of the local hospital and university

- A very close link with the CIC, its leader being one of the PIs of the Unit

- The only group focusing on both neuroprotection and myelin in a translational spirit in the east of France.

The risk-taking factors are :

The evolution of the structure considering human resources since three researchers will have to be replaced; only 40% of the personnel is under 55Y of age, pointing to the urgency to recruit young investigators. Moreover, there is complete absence of administrative personnel.

The reduced number of HDR (8), which seriously limits the unit involvement in the local doctoral school program. The head of the new unit should encourage PIs to undertake the HDR. For the present EA 4438, the absence of an affiliation with INSERM or CNRS also limits their capacity to attract young investigators.

The high diversity of subprojects despite their interest. This could be improved by focusing on the subprojects that have the greatest chance to be transferred to the clinic (see recommendation).

Assessment of the unit's involvement in training:

The head of the unit and several other members are considerably involved in training of post-doc, doctoral and master students and technicians.

The unit has participated in the proposal submitted by the Faculty of Life Science and the University of Strasbourg to obtain from the French Government the national authorization (Habilitation) to deliver the Bachelor's Degree in Cell Biology and Physiology.

Various lab members have supervised master's students. They have also generated a considerable number of PhD theses and some are still ongoing (7).

PhD students will have an active participation in the activity of the new unit by means of meetings, seminars and journal clubs. The new unit will also facilitate the interaction of students with external speakers.

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 [Biopathology of Myelin, Neuroprotection and Therapeutic Strategies]:

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

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**

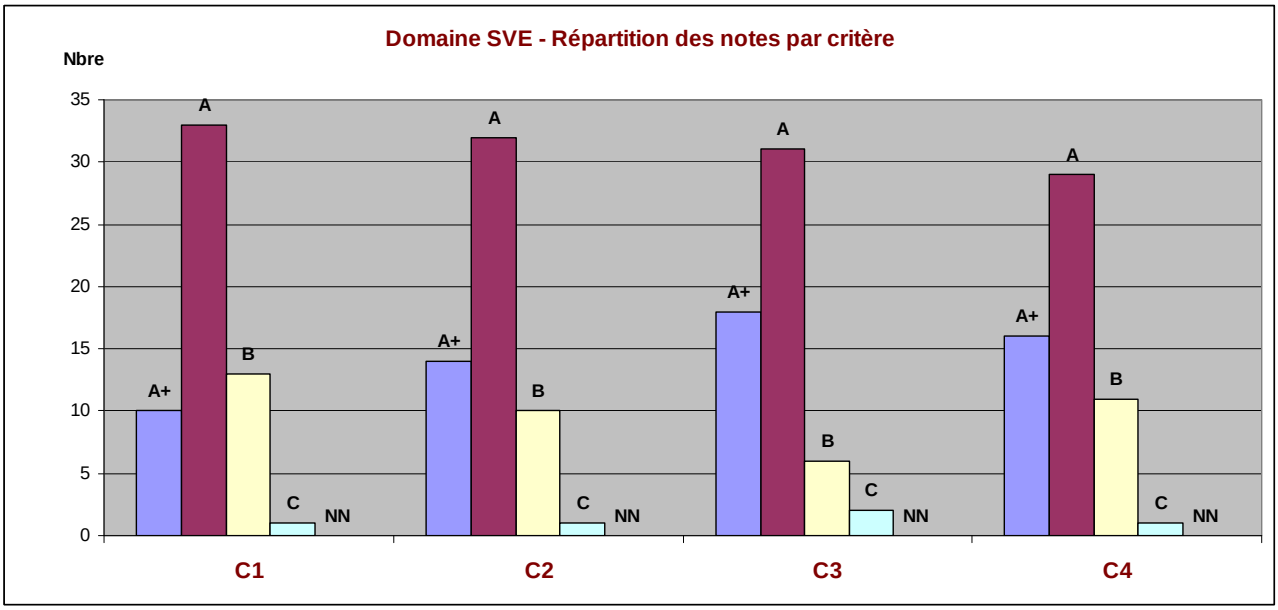
5 • Statistics per field : SVE au 10/05/2012

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	-	-	-	-



6 ● Supervising bodies' general comments

UNIVERSITÉ DE STRASBOURG

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Agence d'évaluation de la recherche et de l'enseignement supérieur (AERES)
20 rue Vivienne
75002 PARIS

Alain BERETZ
Président

Strasbourg, le 25 avril 2012

Objet : Rapport d'évaluation du projet d'UMR_S Biopathologie de la myéline neuroprotection et stratégies thérapeutiques (réf. S2PUR130004562-RT)
Réf. : AB/EW/N° 2012-200

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Direction de la recherche

Cher collègue,

Je vous remercie pour l'évaluation du projet d'unité mixte de recherche (Université de Strasbourg et INSERM) « Biopathologie de la myéline, neuroprotection et stratégies thérapeutiques » porté par Monsieur Ayikoe Guy Mensah-Nyagan.

Vous trouverez ci-joint les réponses du porteur du projet concernant les erreurs factuelles et les remarques et appréciations du comité d'experts.

Je n'ai pas de remarque particulière à ajouter au nom de l'Université.

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 comprenant les observations de portée générale**

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UNIVERSITÉ DE STRASBOURG

Faculté de Médecine

REPLY TO AERES REPORT ON THE PROPOSAL FOR THE CREATION OF A NEW RESEARCH UNIT

Title of the unit: **Biopathology of Myelin, Neuroprotection and Therapeutic Strategies**

Label requested: **UMR Mono-Organisme INSERM**

Project Leader: **Prof. A.G. Mensah-Nyagan**

Dear President and Expert Committee members,
Dear representative delegates from AERES, INSERM, CNU and the University of Strasbourg

We were greatly honored to have our new research unit project evaluated by an international expert committee chaired by and composed of high profile world-class specialists in the field of myelin disorders and neuroprotection. Your detailed assessment and thorough evaluation report clearly point out the fact that our new unit project is an excellent one based on high quality and frequency of publications, strong visibility, recognition, high motivations, local/international integration and on a multidisciplinary approach with excellent interactions between clinical and basic research. Having our efforts recognized by your committee constitutes a strong encouragement for the unit members and we would like to thank you sincerely.

Your report also mentions some weaknesses and risks and provides specific recommendations. We agree with these recommendations and decide to undertake the following actions to counteract the weaknesses and anticipate or circumvent the risks. Each one of your recommendations will fully be considered as described point by point in the sections below.

I) Focus of the new project

In fact, all of the experimental models and subprojects proposed initially derive logically from the scientific background and major results published by the unit members during the 4-year period elapsed. Thus, it appeared natural for us to keep on developing all these models to consolidate data and make significant progress for the translation of results in human clinic. We appreciate the fact that you find all of the subprojects interesting but we agree with your observation indicating that some of the subprojects are more advanced compared to others. In particular, your committee specifically underlines and considers as promising the 3 following research axes and related models: (1) **Chemotherapy-evoked peripheral neuropathies** (Axis-1); (2) **Demyelination/remyelination (myelin repair) in relation to demyelinating diseases such as multiple sclerosis (MS)**(Axis-2); (3) **Neuromyelitis optica (NMO)**(Axis-3). Yes, these 3 research axes are extremely promising indeed. Therefore, we agree with the committee to focus our efforts on these 3 aforementioned subprojects as priorities. Consequently, all of the clinical and basic complementary expertise, multidisciplinary tools available, the unit personnel and financial resources will be devoted to these 3 axes. As suggested by the committee, priority will also be given to the evaluation of therapeutic effects of neurosteroids and thyromimetics. In line with our objectives and specific recommendations of the committee, the unit project is now centered on a single theme (Biopathology of Myelin, Neuroprotection and Therapeutic Strategies) with 3 complementary axes involving the following leaders and principal investigators.

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1-Chemotherapy-evoked Peripheral Neuropathies (Leaders: Mensah-Nyagan AG; Meyer L)
Investigators: Meyer L, Taleb O., Patte-Mensah C, Boehm N, Klein C, Brumaru D, Maître M, Ghandour S, De Sèze J and Mensah-Nyagan AG.

2-Demyelination/remyelination, Myelin Repair and Neuroprotection (Leaders: Ghandour S; Antal C)
Investigators: Antal C, Boehm N, Kemmel V, Samama B, Meyer L, Taleb O, Patte-Mensah C, Trifilieff E, De Sèze J, Mensah-Nyagan AG and Ghandour S.

3-Neuromyelitis optica (Leaders: De Sèze J, Patte-Mensah C)
Investigators: De Sèze J, Trifilieff E, Collongues N, Chanson JB, Rudolf G, Kemmel V, Samama B, Boehm N, Ghandour S, Mensah-Nyagan AG and Patte-Mensah C.

I.1. Axis-1. We will continue our efforts and strengthen our investigations in order to launch shortly a phase I clinical trial to assess in humans the therapeutic action of neurosteroid allopregnanolone against antineoplastic-evoked peripheral neuropathy. We are performing this project in collaboration with the *Centre Regional de Traitement du Cancer en Alsace* (P. Dufour), the *Centre d'Epidémiologie de Strasbourg* (M. Velten), the *Centre d'Investigation Clinique de Strasbourg* headed by J. De Sèze (member and PI in our research Unit) and the Umea Neurosteroid Center in Sweden (T. Backström).

I.2.Axis-2. The unit project will now focus essentially on the model of chronic demyelination in mice as MS model (cuprizone-induced chronic demyelination) to carry out further investigations on demyelination/remyelination mechanisms in order to develop efficient myelin repair and neuroprotective therapeutic strategies. This model of chronic demyelination will particularly be investigated in wild type and nuclear receptor transgenic mice generated at IGBMC. The young MCU-PH recently recruited by our research unit, Dr Antal MC (former PhD student and collaborator of Prof. Chambon P at IGBMC), will strongly be involved in this project. In addition to recurrent funds of the unit, Dr Antal will be supported by specific funds allocated by the Scientific Council of the University of Strasbourg and the CHU. SATT-Conectus, ANR and Neurex applications are also in preparation in order to obtain additional funds to support this promising subproject. A specific effort will also be devoted to strengthen the existing interactions between basic studies and the high-level clinical investigations routinely performed by neurologists of our research unit on national and international cohorts of MS patients.

I.3. Axis-3. As suggested by the expert committee, we will continue to perform a high quality clinical and biomedical research on NMO patients since Strasbourg (neurologists of our research unit) together with Lyon are recognized as Reference Center on NMO. Thanks to the very sensitive biochemical and molecular technological tools routinely used by Dr Patte-Mensah (HDR and PI in the new unit), we will set up a comparative analysis of tissues from the human NMO bio-bank (created by J. De Seze) and NMO animal model to characterize relevant targets and determine useful translational readouts.

II) Human Resources

II.1. Retirement of 3 full time researchers. To solve this question, the Dean and the Scientific Council of the Faculty of Medicine in Strasbourg decided to attribute immediately 2 permanent positions to our Research Unit allowing us to recruit, before the end of the present year 2012, two young permanent investigators: 1 Research Engineer and 1 MCU-PH.

The Research Engineer position is officially published in March 2012 and the recruitment process has started. A first applicant selection will happen in Nice (External National Committee, May 9-11, 2012) and the final selection is scheduled for the middle of June 2012 in Strasbourg. The Research Engineer to be recruited will be involved in the research Axis-1 (Chemotherapy-induced peripheral neuropathies) and the animation of the behavioral platform.

The MCU-PH position is opened to nominate in September Dr Collongues N, a young Neurologist (MD) who obtained his PhD in Neuroscience (under the supervision of Prof. De Sèze) and published

important papers on NMO in highly profiled journals including Neurology (5YIF = 7,518) (2 times) and Arch. Neurol (5YIF = 6,628). Therefore, as MCU-PH, Dr Collongues will continue his research activities on the Axis-3 of our unit project and he will also support our clinical investigations in the *Centre d'Investigation Clinique de Strasbourg* headed by our unit member Prof. De Sèze.

Thanks to a recent grant obtained from the foundation FORNASEP, we appointed a few weeks ago, a young postdoctoral fellow (Susana Brun) to support the research axis on NMO. The Association Ti'Toine (Normandie, France), a permanent sponsor of the team of A.G. Mensah-Nyagan since 2005, has also decided to attribute a 2 year post-doc position to the unit. Recruitment of this postdoc will happen in September. Therefore, the strategy of the unit will consist in supporting the 2 recruited postdocs for full time research positions at INSERM and CNRS. In case our efforts are recognized by INSERM through the attribution to our unit of the label *UMR Mono-Organisme-INSERM*, this label will undoubtedly help us to attract more postdocs with excellent CV and therefore extremely competitive for recruitment at INSERM or CNRS. Also, the strong support of the University of Strasbourg, the Faculty of Medicine and the CHU let us reasonably expect that MCU-PH, Research Engineer and Technician positions will continuously be attributed to the new unit through the next 5-year period to ensure its stability and development.

II.2. Recruitment of administrator and account manager. The Dean of the Faculty of Medicine has clearly indicated to the visiting Committee his commitment to solve this question by attributing an administrator and account manager to the unit as soon as it is created.

II.3. Number of HDR. As pointed out by the committee report (page 9), the unit members "generated a considerable number of PhD theses and some are still ongoing (7)". These positive comments clearly show how active and extremely productive are the unit HDR. In fact the number of HDR will be 8 in 2013 (and not 5 as indicated in the report). However, we agree with the committee that this number will decrease to 7 (in 2014), to 6 (in 2015) and to 5 (in 2017) if nothing is done to anticipate the retirement of the 3 aforementioned full time researchers (see section II.1 above) scheduled successively for the end of 2013, 2014 and 2016. To anticipate and increase the number of HDR, two unit members (V. Kemmel, MCU-PH and O. Taleb, CR1-CNRS) have already started the process to obtain their HDR before the end of this year or early in 2013. In addition, the excellent scientific CV of the 2 young investigators, Dr Antal MC (MCU-PH, 14 publications in highly profiled journals including 4 times in PNAS, 1 Genes Dev and 1 Embo. J) and Dr Meyer L (Faculty Researcher, 18 publications in high level journals such Prog. Neurobiol., Faseb J, Cell. Mol. Life Sci., Glia, Pain…), let us reasonably believe that they will obtain their HDR in the short term. Consequently, we expect that the average number of HDR in the unit during the new 5-year period will be 9.

Overall, we found extremely constructive all of the comments and recommendations made by the expert committee and we have also strongly appreciated the intense scientific and professional discussions we had with committee members during the visit.

Finally, we would like to thank each one of you, Dear President and expert committee members, Dear delegates from AERES, INSERM, CNU and the University of Strasbourg for your time and involvement in the evaluation of our research unit.

Sincerely yours.

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