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MMNP - Maintenance myélinique et neuropathies périphériques

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

Section des Unités de recherche

AERES report on the research unit

Maintenance Myélinique et Neuropathies

Périphériques

From the

Université de Limoges

December 2010



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AERES report on the research unit

Maintenance Myélinique et Neuropathies

Périphériques

From the

Université de Limoges

Le Président de l'AERES

Didier Houssin

Section des unités
de recherche

Le Directeur

Pierre Glorieux

December 2010



Research Unit

Name of the research unit: Maintenance myélinique et Neuropathies périphériques

Requested label : EA

Name of the director: Mr. Benoit FUNALOT

Members of the review committee

Committee chairman

Mr. Bernard ZALC, Université Paris 6, Paris

Other committee members

Ms. Anne Baron VAN EVERCOOREN, Université Paris 6, Paris

Ms. Rebecca MATSAS, Institut Pasteur, Athènes, Grèce

Mr. Bruno BROCHET, Université de Bordeaux 2

Mr. Frédéric DUBAS, Université d'Angers, représentant du CNU

Observers

AERES scientific advisor

Mr. Christian GIAUME

University, School and Research Organization representatives

Mr. Serge VERDEYME, Université de Limoges



Report

1 • Introduction

- Date and execution of the visit :

The visit began at 8:30 am on December 17th 2010 and ended the same day at 5:00 pm. The agenda included the presentation of the unit past activities and project by the head of the unit, presentation of axis 1, presentation of axis 2, and successive meetings with staff members, engineers and technicians, students and post-doc and University of Limoges representatives.

- History and geographical localization of the research unit, and brief presentation of its field and scientific activities

Current activities and projects relating to peripheral nerve are based on the work of the head of the neurology department, who has for several decades developed in Limoges the morphological analyses of peripheral nerves from patients with peripheral neuropathy and corresponding animal models. This initial approach has been progressively implemented by more sophisticated technique such as biological analyses, immuno-EM, and more importantly molecular genetic analyses.

These activities are backed up by the National reference centre for rare peripheral neuropathies (created in 2006), the Departement and laboratory of neurology and the department of biochemistry and molecular genetics.

- Management team: The head of the unit is M. FUNALOT
- Staff members

N1: Number of researchers with teaching duties (Form 2.1 of the application file)	11
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	0
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3PH, 1 AHU
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	6
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	
N6: Number of Ph.D. students (Form 2.7 of the application file)	
N7: Number of staff members with a HDR or a similar grade	8



2 • Overall appreciation on the research unit

- Summary

This is an excellent project relying on the existence of a superb collection of biological samples from patients presenting with a peripheral neuropathy and which have been well characterized clinically and morphologically at the EM. This is probably the best and most competitive french team in the field of peripheral neuropathy.

- Strengths and opportunities

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 ongoing collaboration with the unit at the ENS (Paris) give to this rather clinically oriented team a strong basic research back up. This scientific strategy has to be maintained. The project has a complete support from the University and has been identified as one of the 3 out of 25 projects presented this year that has already been selected by the University (based on the very positive comments by the SAB) to receive 120 k€ for a 3 year period.

- Weaknesses and threats

The experimental therapeutic part of the project needs to be more focussed. The hydrogel part of the project with its strong linked with MedinCell (a biotech company based in Montpellier) has a strong potential. However, the committee recommends the PI to choose one factor (for instance NT3) and carry on all the experimentation to prove the concept, rather than testing a battery of compounds. The high throughput project could be dropped since there is not locally the forces to develop such a costly project. The rhEPO project appears as a service prestation for an israelian company and could as well be abandoned, since the cognitive outcome seems weak. These recommendations, if followed, would allow the principal investigator to concentrate human ressources on less projects and increase dramatically his chances of success.

- Recommendations

The choosen director is an excellent scientist and he has been recognized and accepted by all the participants of the project as well as by the local academic staff as the best candidate to direct the Unit. This put him in the best position to impose to his group the above listed recommandations : namely focus the projects on those where the team is in a position of international leader and for which they have the human and financial forces to conduct the project to the best successful issue.

- Production results

During the past 4 years: 139 papers in journals referenced in PubMed, among them 83 had a member of the laboratory as either first or last author, 26 of which with an IF>5.

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	11
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	0
A3: Ratio of members who are active in research among staff members $[(A1 + A2)/(N1 + N2)]$	1
A4: Number of HDR granted during the past 4 years	4
A5: Number of PhD granted during the past 4 years	11



3 • Specific comments

- **Appreciation on the results**

A major recent finding from this group is that the depletion of Schwann cells and boundary cap cells or inactivation of *Krox20/Egr2*, a master regulatory gene for myelination in Schwann cells, results in transgression of the CNS/PNS boundary by astrocytes and oligodendrocytes and in myelination of nerve root axons by oligodendrocytes. They have analyzed a human patient affected by a congenital amyelinating neuropathy, associated with the absence of the *Krox20* protein in Schwann cells. In this case, the nerve roots were also invaded by oligodendrocytes and astrocytes, which indicates that transgression of the CNS/PNS boundary by central glia can also occur in pathological situations in humans.

In a randomized study against a placebo they have demonstrated an analgesic effect of botulinum toxin (BTX-A) in patients with diabetic painful peripheral neuropathy. A single session of multiple intradermal injection of BTX-A produces long-lasting analgesic effects in patients with focal painful neuropathies and diabetic neuropathic pain, and is particularly well tolerated.

An interesting discovery is the demonstration of mitochondrial abnormalities in axons from neuropathic patients presenting with mutations in *MFN2* et *GDAP1* genes and that severe early-onset axonal neuropathy due to *MFN2* mutations can present as an apparently recessively inherited neuropathy.

For a group of this size there is a good number of publications. However, they are somewhat heterogeneous ranging from *NEJM* to *La presse medicale* or *la revue du praticien*. The team has benefited 2 ANR grants and will deposit 2 new projects to answer the 2011 call.

- **Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners**

Participants to the project receive numerous invitations to participate and communicate during national and international meetings.

One post-doc from Uruguay was recruited last year for 1 year. However, there is no full time researchers, and this year no post-doc.

The members of the unit have obtained 2 ANR grants and have 2 ANR grants pending.

This team has an international reputation. More precisely they have established collaborative programs with Australia, USA (several), Algeria, Spain, Germany....

The committee acknowledges the strong link with the biotech *MedinCell*.

They have monthly seminars with invited speakers from outside Limoges. Based a large part of the project on candidate genes is a real risk, but they like to demonstrate that this risk can pay off !

In addition, concerning the scientific animation, it is of note that they organize once a year a public debate for lay people animated by a media speaker.

- **Appreciation on the management and life of the research unit**

Each group of personnel (researchers, technicians, students) all agrees on the choice of the head of the project. They all appreciate his qualities and none has reported a single conflict. They have a weekly lab meeting.

They have monthly seminars with invited speakers from outside Limoges. Based a large part of the project on candidate genes is a real risk, but they like to demonstrate that this risk can pay off.



In addition, concerning the scientific animation, it is of note that they organize once a year a public debate for lay people animated by a prominent speaker.

Practically all the participants to the project have a heavy load of teaching and they are very active in different activities to support the regional effort of research.

- **Appreciation on the scientific strategy and the project**

This is an excellent project relying on the existence of a superb collection of biological samples from patients presenting with a peripheral neuropathy and which have been well characterized first clinically and then morphologically at the EM level.

Following an evaluation by the SAB from the University of Limoges, a support of 40 k€/year has already been obtained from the University. The SAB strongly recommended to support this team that has been ranked amount the 3 first teams of the University of Limoges.

This is probably the best and most competitive French team in the field of peripheral neuropathy.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
MAINTENANCE MYÉLINIQUE ET NEUROPATHIES PÉRIPHÉRIQUES	A	A	A+	A	A

C1 Qualité scientifique et production

C2 Rayonnement et attractivité, intégration dans l'environnement

C3 Gouvernance et vie du laboratoire

C4 Stratégie et projet scientifique



Statistiques de notes globales par domaines scientifiques (État au 06/05/2011)

Sciences du Vivant et Environnement

Note globale	SVE1_LS1_LS2	SVE1_LS3	SVE1_LS4	SVE1_LS5	SVE1_LS6	SVE1_LS7	SVE2_LS3 *	SVE2_LS8 *	SVE2_LS9 *	Total
A+	7	3	1	4	7	6		2		30
A	27	1	13	20	21	26	2	12	23	145
B	6	1	6	2	8	23	3	3	6	58
C	1					4				5
Non noté	1									1
Total	42	5	20	26	36	59	5	17	29	239
A+	16,7%	60,0%	5,0%	15,4%	19,4%	10,2%		11,8%		12,6%
A	64,3%	20,0%	65,0%	76,9%	58,3%	44,1%	40,0%	70,6%	79,3%	60,7%
B	14,3%	20,0%	30,0%	7,7%	22,2%	39,0%	60,0%	17,6%	20,7%	24,3%
C	2,4%					6,8%				2,1%
Non noté	2,4%									0,4%
Total	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

* les résultats SVE2 ne sont pas définitifs au 06/05/2011.

Intitulés des domaines scientifiques

Sciences du Vivant et Environnement

- SVE1 Biologie, santé
 - SVE1_LS1 Biologie moléculaire, Biologie structurale, Biochimie
 - SVE1_LS2 Génétique, Génomique, Bioinformatique, Biologie des systèmes
 - SVE1_LS3 Biologie cellulaire, Biologie du développement animal
 - SVE1_LS4 Physiologie, Physiopathologie, Endocrinologie
 - SVE1_LS5 Neurosciences
 - SVE1_LS6 Immunologie, Infectiologie
 - SVE1_LS7 Recherche clinique, Santé publique
- SVE2 Ecologie, environnement
 - SVE2_LS8 Evolution, Ecologie, Biologie de l'environnement
 - SVE2_LS9 Sciences et technologies du vivant, Biotechnologie
 - SVE2_LS3 Biologie cellulaire, Biologie du développement végétal

Limoges, le 16 avril 2011

Le Président

à

Monsieur le Président
AERES
20 rue Vivienne
75 002 PARIS

Service Recherche

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OBJET

**General comment for the Unit Maintenance Myélinique et Neuropathies
Périphériques – 0870669E**

Dear Mr President,

We thank the visiting committee members for their thorough evaluation and intense work. We are grateful for their positive comments and fully agree with their recommendations, which will be carefully followed. Namely, we will focus our projects "on those where the team is in a position of international leader". As suggested, the experimental therapeutic part will first be limited to a "proof of concept" study focused on a single compound, without developing a high-throughput project.

Yours faithfully,



J. FONTANILLE