Neuroinflammation : Imagerie et thérapie de la sclérose en plaques

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Neuroinflammation : imaging and therapy of multiple sclerosis

From the

Université Bordeaux 2 Victor Segalen

INSERM (for the project)

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Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

May 2010

Research Unit

Research Unit: Neuroinflammation : imaging and therapy of multiple sclerosis

Requested label : UMR_S INSERM

Director: Klaus PETRY

Members of the review committee

Chairman Committee

Mr Robert MULLER, Univ. Mons, Belgique

Other committee members

Mr Hervé SAINT-JALMES, Université Rennes 1

Mr Ponnada NARAYANA, Univ. Texas, Houston, Etats-Unis

Mr Jean-Philippe RANJEVA, Université de la Méditerranée (Aix-Marseille 2)

Mrs Graciela PAVON-DJAVID, Université Paris 13

Mr Maxime GUYE, Université de la Méditerranée (Aix-Marseille 2)

Committee members suggested by CNU, CoNRS, CSS INSERM, CSS INRA, INRIA, IRD...

Mr Pascal MERLET, CSS INSERM representative

Mr Jean-Marc CONSTANS, CNU representtaive

Observers

AERES scientific advisor:

Mr Christian BARILLOT,

University representative

Mr Alain BLANCHARD, Vice-Président du Conseil Scientifique, université Bordeaux 2

Research organisation representative

INSERM: Marie-Josèphe Leroy-Zamia

Report

1 • Introduction

- Date and execution of the visit

The meeting started on Friday 8.45 a.m., november 13th. The Evaluation Committee listened to the presentation by the director assisted by his team members about the scientific objectives of EA 2966, its structure and organization, and some of the projects that are currently in progress. This University team has applied for an INSERM single-team recognition label. The presentation was followed by series of questions and answers and discussion. Following these presentations, the Evaluation Committee visited the biological and biochemistry facilities and listened to the presentations (posters) by some of the team members. On the afternoon of the 13th, the Evaluation Committee, in a closed door session, discussed their impressions of the center and identified strengths and weaknesses of this research team. This report reflects these deliberations.

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

The university research laboratory "Neurobiology of myelin pathologies" EA2966 was created in 1999 in proximity to the University Hospital Pellegrin. It is located in a two-floor laboratory belonging to the University Victor Segalen Bordeaux-2 that houses the biochemistry facilities (Surface 376 m²).

This interdisciplinary research team is composed of basic scientists (3 biologists/biochemists) and clinical researchers (1 neurologist, 1 neuroradiologist, 1 surgeon). The main focus of this small group is to improve patient management and develop bio-imaging-markers for characterization of Multiple Sclerosis (MS), evaluate various therapies and develop new therapeutic strategies. Application of these methodological breakthroughs is also potentially useful for characterization of other diseases involving neuroinflammation (brain trauma, tumors, stroke).

Members of this team have designed new methodological approaches and integrated protocols to study and reduce nervous tissue inflammation in MS and repair by 1) monitoring and characterizing ambivalent activation profiles of macrophages infiltrating the nervous tissue using MRI in animal and humans; 2) monitoring with MRI, various pathophysiological processes accompanying MS such as blood brain barrier (BBB) permeability, inflammatory lesion progression, molecular alterations, vasogenic edema, demyelination, axonal loss and secondary gliosis; 3) determining molecular alterations of BBB endothelial cells in inflammatory conditions, and monitoring in vivo the immune cell interactions with vascular endothelial cells and their inhibition by peptide ligands; and 4) evaluating and defining the reorganization of neuronal networks following cognitive rehabilitation in MS patients by integrating clinical and cognitive parameters, conventional and advanced MRI acquisitions (diffusion, tractography, MT, cell imaging, fMRI) together with immune and gene expression markers. This research activity is highly dependent on 1) clinical facilities (access to patients) provided by the department of Neurology; 2) clinical MRI facilities provided by the department of Neuroradiology and UMR 5231 and 3) small animal MR imaging facilities provided by UMR 5536.

- Management team

The current team is headed by the Director and the Deputy Director. This management team manages the two main aspects of the research team based on basic science applied to clinical science.

- Staff members (on the basis of the application file submitted to the AERES)

The current staff as indicated in the documents and the oral general presentation is composed of: 1 researcher with teaching duties (1 MC, Biochemist), 3 researchers with teaching duties and clinical activities (3 PU-PH, 1 neurologist, 1 neuroradiologist, 1 surgeon), 2 full-time biologist/biochemist researchers from research organization (2

CR1 INSERM); 3 researchers under contracts (Post-Docs), 1.5 engineers with a tenured position, 1 administrative technician (University Victor Segalen) and 4 PhD students. It is noteworthy that the number of potential PhD supervisors (HDR) is important as regards to the number of students, pointing out the team ability for the training of PhD.

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2	4
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers (Form 2.2 and 2.4 of the application file)	1	3
N4: Number engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	1.5
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0.5	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	4
N7: Number of staff members with a HDR or a similar grade	4	5

2 • Overall appreciation on the research unit

• Summary

The research focus of this small group is truly translational from 'bench to bedside' with a major focus on neuroinflammation, particularly related to multiple sclerosis (MS). Immunology, pathophysiology, experimental/clinical neuroscience and MRI surrogate markers are used concomitantly for a better understanding of the underlying causes and consequences of neuroinflammation in rodent models (EAE) and in MS patients. This integrated approach makes sense. While the EAE model cannot be strictly considered as a perfect model of the human MS disease, it nevertheless is the most commonly used animal model. Some of the researchers of this team have a very high visibility at the national and international levels, especially related to contrast agents, targeting macrophages with USPIO. This topic is concomitantly developed at the pre-clinical (EAE models) and clinical levels. This is the first group that published the administration of USPIO in MS patients. Another strong point is relative to the ability of this team to provide the whole chain to evaluate new therapeutics (collaboration with Merck and Serono) from animal models to humans. Indeed, the clinical research by this group is recognized for the management of MS patients. This team is regularly invited to participate in several international multicenter trials for evaluating the efficacy of new therapeutics. Clinical research is conducted at the interface of neuropsychology and experimental neurosciences, including functional MRI, for better characterization of the cognitive impairment in MS patients, starting from the very early phase into the progressive phase. Finally, innovative and original new molecular biology techniques are being developed by this group (for a new phage display method, pending patent). The scientific productivity is excellent, particularly considering the small size of the group. The management is very effective. It is noteworthy that, due to the excellent and broad training received, all students can easily find employment at the end of their stay in the unit.

• Strenghts and opportunities

This group, composed of a multidisciplinary and researchers with complentery expertise, is one out of two or three groups in France that is capable of conducting real translational projects focused on neuroinflammation. This group has expertise in cutting edge molecular biology for phage display (patent pending). This team has a worldwide leadership (along with the Amsterdam group which is much larger in size) on USPIO application both in animals and humans. This group has also the ability to conduct clinical projects on large cohorts of patients.

- Weaknesses and threats

Although the whole project is focused on neuroinflammation related to MS, this group suffers from limited human resources, especially considering the numerous topics and methods required to develop its program (immunology, MRI on animals and humans, neuropsychology, follow-up of large cohorts of patients (AQUISEP)…). In addition, it is dependent on MR facilities for both animals and humans on other research units who operate these facilities. This may jeoperdise their projects if broader access to the imaging facilities is not guaranteed. Equipement and procedures of the biochemistry laboratory also need to be updated to meet all the cGMP and GLP procedures.

- Recommendations to the head of the research unit

The overall scientific production has been highly appreciated by the committee. Nevertheless the committee stresses the risk of 'loss of their cutting edge leadership 'due to the limited size of this group (especially the tenured research positions). The committee feels that a merger of the unit with one or more units with complementary facilities, especially MR instrumentation and phage display, would greatly benefit it in terms of resource management, scientific visibility, expanded expertise in MR physics and image post-processing (UMR 5536 and UMR 5231) and bringing together technical/theoretical human ressources needed for MR imaging and post-processing. The committee strongly encourages this group to further develop this transversal project on neuroinflammation which may have a positive clinical impact for MS patients.

- Production results

Publication activity is well balanced between basic science and clinical applications. Members of the team are co-authors of high level publications from national and international consortiums.

A1: Number of lab members among permanent researchers with or without teaching duties who are active in research (recorded in N1 and N2)	6
A2: Number of lab members among permanent researchers with or without teaching duties who are active in research (recorded in N3, N4 and N5)	5
A3: Ratio of members who are active in research among staff members [A1/(N1+N2)]	6/6
A4: Number of HDR granted during the past 4 years	1
A5: Number of PhD granted during the past 4 years	2

3 • Specific comments

- Appreciation on the results

The committee highly appreciates the efforts of this group in providing significant advances in understanding causes and consequences of neuro inflammation at multi-scale levels, from cellular to integrated systems in animals and human, and finally to cognitive deficits in humans. The project is relevant, original and coherent with very high impact on the field. This group, composed investigators with multidisciplinary and complementary expertise, is one out of two or three groups in France that is capable of conducting true translational projects from bench to bedside with a focus on neuroinflammation related to MS. This group has a strong expertise in molecular biology in phage display (patent pending). This team is an international leader (along with the Amsterdam group) on the application of USPIO both in animals and humans. This group has also the ability to conduct clinical projects on large cohorts of patients

The quality of publications is excellent with 33 publications in rank A journal during the period 2005-2009. 21 publications directly focused on neuroinflammation in animal models and humans and published in journal with high

impact (Neuroimage, Human Brain Mapping, J Physiology, Brain…), and 5 papers are published in journals such as New England J Med, Lancet Neurol, Ann Neurol and Neurology in collaboration with highly visible national and international consortia involved with large cohorts of MS patients. The other papers are related to new applications mainly concerned with stroke.

This research group has developed a good interface with the clinic (CHU Pellegrin, Bordeaux) and industrial partners (Guerbet, Merck, Serono). This industrial collaboration contributes towards funding PhD students and post-doctoral fellows in various projects.

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

All PhD students trained in this team pursue their academic carrier. Valorization activity of the group allows contractual employments (3 post-Doc/phD students and 1 technician).

High visibility of some of the team members involved in i) basic and clinical uses of USPIO in MS and ii) clinical management of MS patients with participation in national and international multicentre projects for evaluating the efficiency of new therapies.

Valorisation activity of the group allows contractual employments of 7 fellows (technicians, PhD students and post-docs).

This research team generates significant funds from various competitive applications and industrial partnerships:

- ANR TECSAN 2007 - Nanobio imaging : 296k€
- ARSEP 2009 - Peptides ligands : 20k€
- ARSEP 2009 - Cognitive Rehabilitation : 80 k€
- Industrial contracts:
- Guerbet 2005 (5 year contract) 150 k€
- Merck Serono 2006 (1.5 year contract) 352 k€

Members of the research team are part of the European MAGNIMS network (Amsterdam, Milan, Bâles, London …) which aims at developing surrogate markers based on MRI for the better monitoring of MS patients and the Club Francophone de la SEP, a national clinicial network devoted to the care of MS patients.

The committee takes note with appreciation of this group's efforts in the socio-economic landscape with strong partnerships with pharmaceutics (Serono, Merck) and contrast agent manufacturer (Guerbet) for various projects conducted both in preclinical and clinical studies.

- Appreciation on the strategy, management and life of the research unit

All members of the team cooperate to provide the tools and methodology required to achieve the goals from the cellular level (biochemists + biochemistry laboratory) , access to human tissue materials (neurosurgeon + dedicated P2 laboratory room), animal models (animal facilities + local expertise to induce EAE), MS patient recruitment (Neurologist involved in the coordination of the regional clinical network of MS + neuropsychologists), the clinical MRI expertise (neuroradiologist). The only weakness in this organization is related to the limited access to small animal imaging facilities which has to be discussed in the context of the new Bio-Imaging structure and even more in the possible merger of this group with one or more groups with complementary facilities and expertise (UMR 5536 and/or UMR 5231).

Some perplexity has been expressed by the committee about the duplication of efforts by this group and lack of effort to exploit the the outstanding expertise and research environment present at the Victor Segalen Campus and the public health Pellegrin hospital. The committee considers it essential to organize joint meetings before merging with the other research units (UMR 5536 and/or UMR 5231) who share most of the technical expertise in imaging.

4 researchers have significant teaching duty (biochemistry and medical teaching at the medical school of Bordeaux). The full-time researchers participated in specialized groups on inflammation (~15h/year) and public national events (Fête de La Science).

- Appreciation on the project

This group presents translational projects that are in line with their previous work. The research focused on neuroinflammation, especially related to MS. Immunology, pathophysiology, experimental/clinical neuroscience and MRI surrogate markers are used in an integrated manner for better understanding the underlying causes and consequences of neuroinflammation in rodent models (EAE) and in MS patients.

A risk for the feasibility of this highly visible project exists if no guarantee is provided for a broader access to the imaging facilities. Equipement and procedures of the biochemistry laboratory should be updated to meet all cGMP and GLP procedures.

Again, the committee recommends a merger of the unit with one or more units with complementary facilities. This would be beneficial in terms of resource management, scientific visibility, extended expertise in MR physics and image post-processing.

The group generates sufficient funds to conduct the project and allocation of the resources is well thought out. Efforts should be made to increase the human resources especially techniciens and engineers in biochemistry and may be in molecular biology.

The project is highly original. It is in accordance with the competence of the team members. The studies may contribute to improve the diagnostic tools and treatment in MS.

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	A	A	C	A

Monsieur Pierre GLORIEUX
Directeur de la section Unités de recherche
AERES

Bordeaux, le 25 février 2010

Monsieur le Directeur,

Je vous transmets les observations de Monsieur Klaus PETRY, Directeur de l'EA « Neurobiologie des affectations de la myéline » et du projet d'Unité « Neuroinflammation : imagerie et thérapie de la sclérose en plaques », faisant suite au rapport du Comité de visite de l'AERES.

Je vous prie de croire, Monsieur le Directeur, à l'assurance de mes sincères salutations.

Le Vice-Président du Conseil Scientifique,

Alain BLANCHARD

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AERES Report on research unit: "Neuroinflammation: imaging and therapy of multiple sclerosis". - **Response**

We thank the AERES committee headed by Professor Robert MULLER that has evaluated the research activities and project 2011-14 with the requested label UMR_S INSERM of our research unit.

We completely agree with the objective comments concerning the "Strengths" of our research that have been well recognized, and the instructive suggestions.

Concerning the "Weaknesses and Threats" the committee has pointed two major risk factors:

1) the dependency on the MRI facilities managed by other research units for both human and animal observations;
2) the limited number of human resources – permanent staff.

Point 1:

Indeed, we are aware that some aspects our research project depend on MRI facilities that are managed by other collaborating research units.

In regards to experimentation to define and to monitor in vivo neuroinflammatory mechanisms and therapies in animal models, we have developed alternative approaches which are not depending on the MRI facilities. Indeed, we have obtained the total financial support and the technical instruction to develop an alternative approach of intravital videomicroscopy. Furthermore, the integration of our research team in the newly created priority axis "Technologies pour la Santé" of the University of Bordeaux provides access to alternative in vivo tracers (SPECT and PET-Scan).

Furthermore, the creation of the new Bio-Imaging Institute by the University Bordeaux 2 with the acquisition of new MRI facilities will allow a better performance in responding to the demands of the research units for both experimental and human MRI. It should be recalled that our research unit is founding member of this new Institute; a member of our team – Professor Vincent DOUSSET- is head of the organizing team of the facilities and construction, which is programmed during 2010-11.

Point 2:

Since the (ex nihilo) creation of our research unit in 1999, the permanent team members have managed their research mainly by engaging PhD students, post-docs and technical personal under contracts (mainly research contracts with pharma-industry and ANR). Three new academic researchers have joint the team in last years. There were several technical personal from INSERM interested to join our team, especially after the reorganization and closing of local research units in Neurosciences. However, as a University Research Unit, which is recognized by the French Minister of Research and Technologies, we had no possibility to integrate technical personal from INSERM or CNRS into our team. It should be recalled that two members of the team are full time INSERM researchers. Upon many requests, the University Bordeaux 2 has transferred the first (and single) technician to our team only in 2007. We hope that with the new quadrennial and the reorganisation of research units, the demands of our team will have priority to engage permanent personal to help in realizing our research program. The proposed fusion with other teams of the CNRS will not help in resolving this problem of attributing permanent staff members to our team and research project.

Klaus Petry
Head of research unit