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Neuropathies du système nerveux entérique et pathologies digestives : implication des cellules gliales entériques

Rapport Hcéres

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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
Neuropathies du Système Nerveux Entérique et
Pathologies Digestives
From the
Université de Nantes
INSERM

January 2011



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From the
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Le Président de l'AERES

Didier Houssin

Section des unités
de recherche

Le Directeur

Pierre Glorieux

January 2011



Research Unit

Name of the research unit: Neuropathies du System Nerveux Enterique et Pathologies Digestives

Requested label : UMR_S INSERM

N° in the case of renewal : 913

Name of the director: Mr. Michel NEUNLIST

Members of the review committee

Committee chairman:

Ms. Nathalie VERGNOLLE, INSERM UMR-1043, Université Toulouse 3, France

Other committee members:

Mr. Alan J BURNS, University College London, London, UK

Mr. David GRUNDY, University of Sheffield, Sheffield, UK

Mr. Bruno BONAZ, CHU Grenoble, Université Grenoble 1, France

Ms. Fabielle ANGEL, INSERM U575, Université de Strasbourg, France

Ms. Eva EKBLAD, Lund University, Lund, Sweden

Mr. Eamonn QUIGLEY, University College Cork, Cork, Ireland

Mr. Philippe MARTEAU, Lariboisiere Hospital, Paris France, CNU member

Mr. Marc LABURTHE, Centre de Recherche Biomedicale Bichat-Beaujon, CSS member

Observers

AERES scientific advisor:

Mr. Jean GIRARD



Report

1 • Introduction

- Date and execution of the visit:

The site visit took place over one day on January 12th 2011. The committee assisted as a whole at all interviews and presentations. The chairman worked in close collaboration with all members of the committee to present the present final report.

The visit was well organized and allowed each committee member to have enough time to be able to listen to the presentations, to assess the research performed by the group, to meet with scientists, students and technical personell, as well as with representatives of the local research organizations (regional delegate of the INSERM, delegate of the Hospital, and representative of the University of Nantes). At the end of each presentation, sufficient time was taken to allow discussion between panel members and presenters. At the end of the visit, sufficient time was also taken for members of the committee to discuss and summarize the salient issues to retain for the present report.

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

This research unit was originally created in 2008, perpetuating the themes developed in the Neurogastroenterology Unit U539 (2004-2007). The unit is part of the Institute of Digestive Diseases (IMAD: Institut des Maladies de l'Appareil Digestif), which is an hospital-based institute. The unit is located within the CHU HD of Nantes.

The research is devoted to the study of the role of enteric nervous system, and in particular enteric glial cells, in health and diseases. The Unit being composed of both basic scientists and clinician scientists, the scientific approche uses integrated basic and translational research.

- Management team

The unit applying for renewal will include about 20 staff members initially (scientists, clinician scientists, clinicians, research assistants, technicians and trainees). The unit will be headed by M. M. Neunlist, no deputy director was identified. The director has formed a laboratory council which is composed of researchers, one representative of the technicians and one representative of the trainees. The director is in charge of the management and all aspects related to the organization of the unit. No specific rules have been described for the financial and administrative management of each project.

The laboratory council meets regularly and decides collegially on organizational issues of the center, including prioritization of research projects.

As for scientific interchange, laboratory meetings are organized on a weekly basis, where research-in-progress reports are presented by scientists and trainees, each presenting 2 to 3 times a year. No formal seminar series are organized within the unit, but access to seminars organized by the gastroenterology institute (IMAD) is available.

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	7	6
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	3
N3: Number of other researchers including postdoctoral fellows (Forms 2.2, 2.4 and 2.7 of the application file)	4	5
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	0
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	4	
N6: Number of Ph.D. students (Form 2.8 of the application file)	8	
N7: Number of staff members with a HDR or a similar grade	7	6



2 • Overall appreciation on the research unit

- Summary

Overall, the unit is very productive considering the number of full-time researchers that compose this unit. The unit occupies a unique and original position in the scientific landscape related to Gastroenterology, focusing on the neuro-glial-epithelial unit. Clearly the research performed in this unit is of international standard, and the researchers have established the necessary collaborative links nationally and internationally to perform original research. Overall, this unit represents an excellent model of collaboration and complementarity between basic scientists and clinicians.

- Strengths and opportunities

- The publication record in terms of number and quality of publications is very good. It is important to note that both the number and impact of publications have increased steadily of the past years.
- The unit, by its very nature, holds very close links with clinical research, providing unique conditions to run successful translational research programs.
- The vibrant clinical-research environment has a major impact and constitutes an important factor in attracting and sustaining clinician involvement in basic research.
- National and international collaborations are in place to support the research program.
- Sufficient space has been identified and allocated to the unit, that would also allow the unit to grow significantly.

- Weaknesses and threats

- The number of full-time basic scientists is relatively low in this unit, with only three full-time researchers, as of today. One of them is the director who necessarily devotes some time to the Unit management, another one should retire 2-years after 2012, and one full-time young investigator has been recently recruited. Increasing the number of full-time basic scientists should be considered as a major priority, considering the ambitious nature of the research projects described for this renewal, and the number of “hands and brains” necessary to supervise those projects.
- Related to the previous remark, no technical staff with permanent positions have been allocated to that unit. This aspect is fundamental to sustain continuity of expertise within the laboratories. The recruitment of full-time permanent technical staff to the unit will be essential to their future scientific success.
- Being a relatively small research unit so far, no formal procedures and rules for general management of funds, research priorities, or career development are in place. It was felt by the committee during the visit, that all staff members were satisfied with the present organization and management. With the anticipated increase in the number of persons composing this unit, a more formal organization and management could be put in place.

- Recommendations to the director

- Pursue discussions with the institutions: INSERM, the Hospital and the university, in order to obtain dedicated technical positions. In particular, the University of Nantes, who's representative indicated to the committee the possibility of providing permanent contracts to technical staff who have been employed for more than 6-years (one of the staff members is in that situation).

- Production results

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	9
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	10
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 (Form 2.10 of the application file)	2
A5: Number of PhD granted during the past 4 years (Form 2.9 of the application file)	5



3 • Specific comments

- **Appreciation on the results**

This research unit is centered around the study of the neuro-glial-epithelial unit. The research performed is highly original. The organization of the unit provides a very successful translational research platform, where clinician scientists and basic science researchers interact most extensively and efficiently.

The quality and number of scientific communications are being regarded as excellent, especially, considering the number of full-time PIs. Each year, the unit has published a number of research articles in journals of impact factors superior to 9 (Gastroenterology, Gut, J. Clin. Invest., etc.).

The unit has brought important new knowledge on the functional importance of enteric glial cells in human digestive diseases. In particular, they have demonstrated the role of enteric glial cells in intestinal permeability (publications in Gut and Gastroenterology), in cell to matrix adhesion and intestinal cell proliferation. Overall, the work performed within the Unit has led to the new concept that enteric glial cells are major protective actors in gut pathologies.

The unit has established stable and fruitful collaborations locally, nationally and internationally.

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

The visibility and scientific impact of members of the unit is extremely high to very good for the PI.

It should be emphasized that the unit has attracted a young and productive tenure-track scientist in the past year. Further recruitment of basic scientists should be fostered.

While on the surface it would appear that the unit has had limited success in attracting foreign trainees, this can be attributed, at least in part, to the French system of recruitment and the location of Nantes, remote from the major axes and from Paris.

The ability of the unit to raise funds has been very good, and has been impressively increasing steadily over the last years. Individuals should be encouraged to apply for European funds and to compete for higher levels of funding. Successful links with industry have been established (with Danone).

The unit has established good local and national scientific networks that should be nurtured in the future. Good relationships with the educational structures and public awareness activities were also noted, and should be maintained in the future.

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

The director has good leadership skills, and from the site visit, the committee felt that the director was highly regarded by all staff members. It was particularly impressive to note the friendly and very collegial atmosphere among all staff members. The panel was especially impressed by the very strong collaborative spirit that obviously existed between basic science and clinical researchers. Scientific exchange is adequate through weekly lab meetings and seminar series in the clinical department (IMAD).

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

The research unit has unique strengths to study the biology of glial cells in the gut. A number of projects in different areas were presented. They were all supported by solid preliminary data and their relevance to biomedical research was strong. Overall, good proof of concept towards feasibility was provided. The overall impression of the committee was that the scientific strategy should try to consolidate basic science aspects and to resist the temptation to embark prematurely on related clinical projects until the scientific basis and relevant techniques have been firmly established and validated. The committee acknowledges the presence in the scientific project of cutting edge research.

In conclusion, the committee felt that the Unit 913 is a very good research unit, with scientific productivity of international relevance.



Project 1: Neuro-glial-epithelial unit: Patho-physiological mechanisms and therapeutic targeting during IBD. *Project leaders: A. Boureille, Malvyne Roli-Derkinderen*

The originality of the research proposed is extremely high. The unit is recognized worldwide for its work in the domain of neuro-glial-epithelial cell interactions. Although the theme of IBD is relatively recent for the team, some publications and important preliminary data have been generated. In addition, partnerships and collaborations have been put in place to efficiently address the questions raised in the project. The project is based both on clinical studies and a basic science project.

- Conclusion

- Summary

The project is extremely original particularly from the perspective of studies on enteric glial cells. It is supported by interesting preliminary results although those results are mostly based on IBS. Several questions are addressed in the project and different directions are proposed both from a clinical and basic science perspective.

- Strengths and opportunities

- The studies on glial cell biology are unique and the research unit is recognized worldwide for its studies in the domain
- The technology to study glial cell biology is well established.
- Good interactions between basic science and clinical science are feasible and should permit the performance of good translational research
- Well in line with the missions of the INSERM

- Weaknesses and threats

- The clinical project seems a bit premature at this point. Validation of the techniques proposed to measure permeability *in vivo* in patients employing an endoscopic approach should be performed.
- More preliminary data generated from archival biopsies from IBD patients would be appropriate before starting clinical studies.
- The plans for basic, translational and clinical investigation are commendable but may be overly ambitious given the modest size of the group.

- Recommendations

The project would benefit from a greater focus on glial cell biology since this is the most original part of the project. Basic science studies focusing on cellular and molecular aspects (signaling molecules) of enteric glial cell physiology should be encouraged.



Project 2: Neuro-glial-epithelial unit in Parkinson's disease, *Project leader: P. Derkinderen*

This team has been productive in the area of studies of the enteric nervous system in Parkinson's disease patients, publishing in very good journals (Gut 2008, NG&M 2009, PlosOne 2010, etc.). This scientific production has enabled that team to have an impact in the field, raising their visibility internationally. The group has established the necessary collaborations to be able to consolidate their multidisciplinary approaches (human biopsies, primate tissues, autopsy tissues, mouse models, etc.). The group is also very successful at raising funds. The project to investigate enteric nervous system lesions is very relevant, logical and has achievable objectives.

- **Conclusion :**

- **Summary**

- The proposal sets out a series of experiments to address a very interesting area of investigation, with a high relevance. The project is well balanced between "safe" aspects (autopsy tissues), and more "risky" hypothesis (mechanisms of regulation, alpha-synuclein).

- **Strengths and opportunities**

- Combination of a number of different approaches and tissues to answer important questions.
 - Good visibility of the group
 - Good translational research
 - Good technology transfer potential with the potential to develop new diagnostic biomarkers

- **Weaknesses and threats**

- Colonic biopsies contain ganglia restricted to the sub-mucosal layer of the colon and may not be entirely sufficient to completely delineate all of the changes in the enteric nervous system associated with Parkinson's disease over time. Myenteric ganglia are more likely to be the primary neurons affected by Parkinson's disease pathology; the researchers seem aware of this limitation and have strategies to address it.

- **Recommendations**

- Careful examination of the enteric nervous system from Parkinson's disease patient autopsy tissues should be performed as a priority to further validate the appropriateness and limitations of colonic submucosal ganglia tissues.

- Different regions of the gut could be examined and compared (foregut, mid-gut, colon) for potential variations in severity of the changes of the enteric nervous system.

- The effects of deep central neurostimulation could be studied on the neuro-glial-epithelial unit response in the context of Parkinson's disease. Similarly, the effects of intestinal epithelial barrier reinforcement could be investigated.



Project 3: Nutritional targeting of the neuro-glial-epithelial unit, *Project leader: M. Neunlist*

The general aim of this project is to determine the extent to which the luminal environment, in particular the nutrient content, impacts on enteric neuron biology and thereby on digestive tract function. Relatively few publications related to nutritional influences on the enteric nervous system have been generated by the team so far since this is a new direction. However, in general, the number and quality of publications by the team in the domain of enteric nervous system biology is excellent. Considering the project presented and the means that have been allocated to this project, it is likely that a good scientific production will be associated to this project.

- **Conclusion :**

- **Summary**

This project brings together an internationally recognized team with complementary expertise to investigate important questions about dietary influences on gastro-intestinal functions. Gastro-intestinal disorders have enormous societal impact and a better understanding of the influence of diet, that could definitively be achieved through the present project, could lead to new therapeutic options.

- **Strengths and opportunities**

- Good complementary expertise on the project with in vitro, in vivo models and clinical partners.
 - The approach uses state-of-the-art techniques to investigate enteric-glial-epithelial interactions.
 - Strong translational element bringing together clinician and basic scientists.
 - Collaboration with industry is in place and fully allows the researchers to publish their findings. Contracts of collaboration have already been put in place through INSERM-transfer, and the commitment of the industrial partner was felt to be strong.

- **Weaknesses and threats**

- The project should consolidate the basic science aspects before considering studies in patients with diabetes and obesity.
 - The project is ambitious and would necessitate clear leadership, particularly in making strategic decisions regarding scientific direction.

- **Recommendations**

Considering the ambitious nature of the project as a whole, some themes should be prioritized. For instance, more emphasis should be put on the part of the project focusing on the maturation of the enteric nervous system and the characterization of the neuro-glial-epithelial unit. The clinical project on obesity and enteric nervous system function should be deferred until the former has been completed and experience gained from it utilized to maximal benefit.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
NEUROPATHIES DU SYSTEME NERVEUX ENTERIQUE ET PATHOLOGIES DIGESTIVES	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