



LPPD - Physiopathologie et pharmacologie clinique de la douleur

Rapport Hcéres

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

Section des Unités de recherche

Evaluation report

Research unit

Pathophysiology and Clinical Pharmacology
of Pain

University Versailles-Saint-Quentin en
Yvelines



March 2009



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et de l'enseignement supérieur

Section des Unités de recherche

Evaluation report

Research unit

Pathophysiology and Clinical Pharmacology of Pain

University Versailles-Saint-Quentin-en-
Yvelines

Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

March 2009



Evaluation report



The research unit :

Name of the research unit : Pathophysiology and Clinical Pharmacology of Pain

Requested label : UMR_S INSERM

N° in case of renewal :

Head of the research unit : M. Didier BOUHASSIRA

University or school :

University Versailles-Saint-Quentin en Yvelines

Other institutions and research organization:

INSERM

Date of the visit :

January 29, 2009



Members of the visiting committee

Chairman of the committee :

M. Rolf-Detlef TREEDE, University of Heidelberg, Mannheim, Germany

Other committee members :

M. Per HANSSON, Karolinska University Hospital, Stockholm, Sweden

M. Luis GARCIA-LARREA, Université Lyon 1, France

M. Radhouane DALLEL, Faculté de Chirurgie Dentaire, Clermont-Ferrand, France

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

Ms Marie VIDAILHET (INSERM CSS)

Observers

AERES scientific representative:

M. Pierre-Hervé LUPPI

University or school representative:

M. Gérard CAUDAL, University Versailles-Saint-Quentin en Yvelines

Research organization representatives :

Ms Nicole HAEFFNER-CAVAILLON, INSERM

Ms Christine RULLIAT, INSERM



Evaluation report



1 • Short presentation of the research unit

Number of lab members : 18 including

- 1 full-time researcher
- 3 researchers with teaching duties (PU-PH)
- 4 clinicians (PH) who can do part-time research
- 4 technicians and administrative staff consist, all permanent position INSERM
- 6 PhD students, half of them on external funding including one medical student who has received an Ecole de l'INSERM fellowship

One student has obtained his/her PhD during the past 4 years

Number of publishing lab members : 4 out of 4

2 • Preparation and execution of the visit

The visiting committee had access via the AERES website to the bilan and projet documents. The following strengths and weaknesses were identified based on the written documents :

- Strengths : development of innovative and internationally recognized questionnaires for neuropathic pain screening, RIII reflex studies based in a strong French clinical neurophysiology tradition, pharmacological trials in humans testifying to an excellent clinical research infrastructure.
- Weaknesses : relatively vague conclusions on pathophysiological mechanisms or neuroanatomical pathway, little interaction with basic science laboratories, French tradition of DNIC mechanistic studies could be manifested more strongly, rTMS study with limited news value.
- Opportunities : outstanding epidemiology data forthcoming, impact on clinical practice, more human pharmacology, excellent patient access.
- Threats : lack of basic science roots may endanger translational research, extensive cooperation with the pharmaceutical company Pfizer may be viewed as dual funding or a potential source of bias.

A list of questions was prepared based on these data and was specifically addressed during the site visit. The oral presentations clarified a large number of open questions in a satisfactory manner, e.g. relating to pathophysiological mechanisms of the investigated phenomena (brain mechanisms in nociception), the capacity and expertise to do the proposed diffusion tensor imaging of spinal tracts, and details of the aromatase inhibitor study. After the oral presentations and discussions, the assessment of weaknesses and threats was modified as follows :

- Weaknesses : More pathophysiological concepts were discussed than had initially been offered, including a detailed account of DNIC and other descending control systems. Nevertheless, the number of hypothesis driven studies should be increased and hypotheses should be spelled out more precisely. Upon questioning, the team revealed a good understanding of rTMS state of the art, to the full satisfaction of the visiting committee. Low level of interaction with basic science labs remains a relative weakness.
- Threats : Low level of interaction with basic science labs also remains a threat to future developments in translational research. The international members of the visiting committee learned during the meeting, that acquisition of external funding from industry is an explicit objective for INSERM units. Thus, the five ongoing epidemiological studies funded by Pfizer and one funded by Sanofi-Aventis are now considered as Strengths and Opportunities of the unit and not as a threat.



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

There has been a steady production of publications with an increasing trend over the past 6 years. Publications are of very good quality and include many papers in the leading journals of anaesthesiology and neurology (rated as 4). Numbers of citations also increased steadily reaching nearly 290 in the year 2008. The H-index of the unit director (born 1960) is an excellent 29.

Year	2003	2004	2005	2006	2007	2008
Original papers	5	8	7	8	5	11
Reviews, editorials	1	3	0	5	4	3

The research unit has excellent links with national partners, including a regional network (Ile de France) that enables highly efficient patient recruitment for all three major types of pain (nociceptive, neuropathic, “dysfunctional”). Links to patient associations (Fibromyalgia, Syringomyelia, Glossodynia) have been established. To cover such a range of pain conditions is exceptional at an international level, represents a first-class logistical and intellectual achievement, and is only possible with such an interdisciplinary team (neurology, anaesthesiology, rheumatology, gastroenterology, psychology). The local network also allows the unit to employ a wide range of methods not available at the hospital where they are based (e.g. fMRI). The unit has been able to attract an impressive level of outside funding from pharmaceutical companies, both for clinical trials and for epidemiological studies.

Links with international partners are less prominent and have so far led to only three original publications (with partners from Brazil, Spain, USA). Nevertheless, the unit has achieved high international visibility and recognition, in particular regarding development of questionnaire tools to screen for neuropathic pain (translated into several languages), performance of state-of-the-art clinical trials and human pharmacology. Noteworthy achievements include the identification of predictors for response to i.v. lidocaine in neuropathic pain and a series of studies into irritable bowel disease that identified subgroups based on inhibition vs. sensitization patterns and the response to a 5HT agonist.

With respect to past achievements, international visibility and relevance of some of the work (questionnaire tools, guidelines) are outstanding (rated 5), but originality and relevance of research activity are mixed depending on subproject (range 3-5, overall rating 4).

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

Four of the planned projects were evaluated as representing particularly strong points, the first two (IBS and aromatase projects) having the potential for outstanding front-line high-risk projects :

- Irritable Bowel Syndrome (IBS) : continuing the excellent and highly cited previous work on two subgroups of IBS (pain sensitivity sensitized or inhibited by rectal distension) the unit plans to do fMRI studies focussed on potential changes in prefrontal cortex activity. Furthermore, a hypothesis on different gut microbes in these subgroups will be pursued.
- Aromatase inhibitors for breast cancer : based on reports that up to 50% of women receiving this adjuvant treatment develop widespread pain, the unit proposes to study this phenomenon as a model for fibromyalgia. This project represents an innovative approach, and the unit has the logistics to perform the study.
- Syringomyelia : the unit has contact with a large group of patients with this type of spinal lesion. The proposed project has great potential to clarify several questions around the anatomy of human pain pathway. The addition of DTI and LEP to the methods spectrum of the unit is appreciated. We suggest to measure the N13 of SEP and to do below-lesion stimulation to assess the long tracts.



- Minocycline to prevent chronic pain following low-back surgery : This is a substance that inhibits microglia and is available for use in humans. Hence this project directly addresses a current hypothesis from animal research.

The following projects were seen less favourably :

- The project on Botulinum toxin is considered more of an efficacy trial than a mechanistic trial. The microneurography study component is considered unrealistic, since microneurography is a very-low-yield technique.
- The project on pain due to lateral femoral cutaneous nerve damage during bone harvesting needs some redesign, including electrophysiological assessment of nerve damage and other parameters to quantify the extent of proximal nerve lesion. The current focus on distal parameters in the skin appears unbalanced given the proximal site of nerve damage.

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

Given the limited local resources at the hospital where the unit is based, much has been achieved by creating an extensive regional networking throughout Ile de France region and by acquiring several large grants from industry. This network supplies interdisciplinary expertise and outstanding patient recruitment capacity. The University of Versailles has created its medical faculty in 2001. Currently, it has two INSERM units. Therefore, performance of this clinical pain unit plays an important role in the future development of the Faculty of Medicine and the university is committed to pain research. On the down side, there is no additional space available locally (but in 2011 at another campus) and additional permanent positions for promising young researchers are not yet available. The increased flexibility of the university budget as of 2009 may possibly be used to create space and positions.

The regional network structure is a potential threat at the educational level, because about half of the students can only interact with their advisors during laboratory meetings twice a month. Those students based at the hospital itself greatly appreciated the daily contacts, particularly with two of the principal investigators who guided them through many difficult steps in their thesis work. The students also appreciated funding to attend conferences such as the World Congress on Pain in Glasgow. Although there seems to be a rule that students are first authors on their papers, the committee was surprised by the low number of student authored publications (total of 6: two had two papers, and two others had one paper each). A formal training for students in laboratory techniques or scientific reading and writing seems also to be lacking currently. That only one PhD and one Master thesis were completed in the past four years may be related to the clinical environment, i.e. many candidates do only part-time research.

As to the category of "promising young researchers", the internationally recognized members of the unit are clinician researchers over 40y of age. No permanent positions are available at the University for young researchers. On the other hand, one Ecole de l'INSERM student and one former student from abroad (returned home) are promising at their intellectual level.

Technicians & administrative staff : 4 CDI out of 4 (all permanent position INSERM consisting of 1 secretary / 1 neuropsychol / 2 research technicians (ex-electrophysiol)). Specific formation for the two latter on clinical research protocols (as Clinical Research Assistants (ARC). Every 15 days there are plenary meeting of the team: communication passes well and all technicians know the different ongoing protocols and experiments. All consider their career evolution as favourable (best than before entering this lab). Task distribution and independence in work organisation are appreciated, as well as the full trust by the Unit director. Only one person for organizational / administrative purposes (secretary - organizer) : this may be a limiting factor if the unit is to increase in size.

Prospects for long-term viability are very good. The unit has built a strong network with part-time clinician researchers; but depend strongly on single INSERM funded researcher.



6 • Recommendations and advice

— Strong points :

- excellent patient recruitment in an exceptionally wide range of pain conditions
- in difficult field of “dysfunctional pain syndromes”: strong background on IBS subgroups and mechanism-driven new projects (fMRI and microbes)
- strong epidemiology, strong human pharmacology studies

— Weak points :

- ratio of descriptive projects versus hypothesis driven projects
- little interaction with basic science groups

— Recommendations :

- more hypothesis-driven studies should be performed
- focus on smaller range of topics
- more interaction with basic science for forward and reverse translation
- get involved in doctoral school (formal lectures and courses for graduate students) for biologists etc.
- put international collaboration on level of joint publications
- need permanent positions for 1-2 young promising researchers (university and/or INSERM)
- interface program hospital/INSERM
- 2009 may possibly be used to create space and positions

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	B	A



UNIVERSITÉ DE VERSAILLES SAINT-QUENTIN-EN-YVELINES

LA PRESIDENCE

Versailles, le 7 avril 2009

La Présidente de l'Université de
Versailles Saint-Quentin-en-
Yvelines

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à

Monsieur Pierre GLORIEUX
Directeur de la section des unités
de recherche à l'AERES

Objet : Evaluation UMR INSERM/UVSQ U792 - Laboratoire Physiopathologie et
Pharmacologie Clinique de la Douleur

Monsieur,

Ayant pris connaissance du rapport d'évaluation de l'AERES communiqué le 26 mars 2009 concernant le laboratoire Physiopathologie et Pharmacologie Clinique de la Douleur, je vous adresse ci-dessous les commentaires du professeur Didier Bouhassira, directeur de cette unité mixte de recherche et du professeur Gérard Caudal, vice-président du conseil scientifique à l'UVSQ :

➤ **Commentaires du directeur de laboratoire :**

The director thanks the members of the committee for their comments and constructive suggestions.

Regarding the comment about students in paragraph 5 ("Appreciation of resources and of the life of the unit"), he would like to specify that the number of master theses completed over the 4 past year was not one but seven. Four of these students (E. Pelle-Lancien, F. Plantevin, F. Martin, X. Moisset) signed at least one publication as first or second author. The other students (C. Debes, F. Nahmias, A. Wozakiewicz) are first or second author of publications submitted or in preparation.

➤ **Commentaire de l'UVSQ :**

Le rapport du comité d'experts de l'AERES signale le besoin de ce laboratoire de recruter de jeunes chercheurs. Du fait du rattachement récent de la faculté de médecine à l'UVSQ (en 2002), un certain nombre d'enseignants-chercheurs hospitalo-universitaires de l'UVSQ effectuent aujourd'hui leur recherche dans des unités non rattachées à l'UVSQ, notamment dans Paris intra-muros. Au cours des années à venir, le redéploiement de ces postes sera en priorité en faveur des laboratoires de médecine rattachés à l'UVSQ, dont bien sûr celui-ci, si bien que des opportunités de recrutements de permanents sont à attendre

pour les prochaines années. Le développement des partenariats industriels, dans lesquels cette unité est fortement impliquée, est par ailleurs encouragé par l'UVSQ, et une attention particulière est portée au soutien des unités mixtes de recherche avec des EPST. L'UVSQ a donc toutes les raisons de poursuivre son soutien à cette UMR dans les années à venir.

Je vous prie de croire, Monsieur le Directeur, à l'expression de ma respectueuse considération.

