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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

Department for the evaluation of
research units

AERES report on unit:

Pathophysiology and Clinical Pharmacology of Pain

LPPCD

Under the supervision of the following
institutions and research bodies:

Université de Versailles Saint-Quentin-en-Yvelines -

UVSQ

Institut National de la Santé Et de la Recherche

Médicale - INSERM

January 2014



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

Department for the evaluation of
research units

*On behalf of AERES, pursuant to the Decree
of 3 november 2006¹,*

- Mr. Didier HOUSSIN, president
- Mr. Pierre GLAUDES, head of the
evaluation of research units department

On behalf of the expert committee,

- Mr. Luis GARCIA-LARREA, chair of the
committee

¹ The AERES President "signs [...], the evaluation reports, [...] countersigned for each department by the director concerned" (Article 9, paragraph 3 of the Decree n ° 2006-1334 of 3 November 2006, as amended).



Evaluation report

This report is the result of the evaluation by the experts committee, the composition of which is specified below.

The assessment contained herein are the expression of independent and collegial deliberation of the committee.

Unit name:	Physiopathologie et pharmacologie clinique de la douleur.
Unit acronym:	LPPCD
Label requested:	INSERM - UVSQ
Present no.:	U 987
Name of Director (2013-2014):	Mr Didier BOUHASSIRA
Name of Project Leader (2015-2019):	Mr Didier BOUHASSIRA

Expert committee members

Chair:	Mr Luis GARCIA-LARREA, Center for Neuroscience of Lyon
Experts:	Ms Marie-Bernadette DELISLE, C.H.U Rangueil Toulouse (representative of CSS INSERM) Mr Alain ESCHALIER, Université d'Auvergne Clermont-Ferrand, France Mr Troels Staehelin JENSEN, Aarhus University Hospital, Denmark

Scientific delegate representing the AERES:

Mr Yves TROTTER

Representatives of the unit's supervising institutions and bodies:

Mr Etienne HIRSCH, Institut National de la Santé Et de la Recherche Médicale
Mr Frédéric LOFASO, Université de Versailles Saint-Quentin-en-Yvelines
Ms Monique COHEN, Université de Versailles Saint-Quentin-en-Yvelines



1 • Introduction

History and geographical location of the unit

UMR 987, entitled « Pathophysiology and Clinical Pharmacology of Pain », is a mixed Inserm/UVSQ single theme ('mono-thématique'), single team ('mono-équipe') research unit hosted by Assistance Publique Hôpitaux de Paris (AP-HP) at Ambroise Paré University Hospital in Boulogne-Billancourt (Paris Île-de-France West Medical Faculty). The research activities of this group are exclusively devoted to clinical research and include studies both in patients with acute (postoperative) or chronic pain syndromes and in healthy volunteers.

The Pathophysiology and Clinical Pharmacology of Pain laboratory was formed at the end of the 1990s by a small group of clinician researchers specialized in pain medicine, with a training in both clinical and basic research. The main objective of this group has been to develop research programs focused on patients, as such studies were largely lacking in France. The group, which has been located since its creation at the Pain Clinic of the Ambroise Paré Hospital in Boulogne-Billancourt, has rapidly expanded to become truly multidisciplinary, and the medical team has been reinforced by the addition of technicians, scientific officers ('ingénieurs') and students. The group was recognized and accredited as a mixed research unit ('UMR') by Inserm and Université Versailles Saint-Quentin-en-Yvelines (UVSQ) in 2002 (UMR 332), and was renewed in 2006 (as UMR 792). Following another AERES assessment in 2009, the group was again recognized as an UMR by Inserm and UVSQ in 2010 as UMR987.

Management team (tenured positions)

As tenured/permanent positions the unit includes 1 director of research (DR1 Inserm), 5 full professors (PUPH), 1 associate professor and 2 hospital doctors (PH). This multidisciplinary medical team (neurologists, anesthesiologists, rheumatologists, gastroenterologists) is assisted by 2 scientific officers ('ingénieurs'), 1 research technician and 1 secretary from Inserm. The unit director (DB) ensures the general coordination, overall goals and scientific objectives of the team. Each specific research topic is then under the coordination of one or two senior members, themselves responsible for the supervision of juniors and PhDs.

AERES nomenclature:

SVE1-LS4

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors (PUPH) and similar positions (PH)	6	6
N2: Permanent researchers from Institutions and similar positions	1	1
N3: Other permanent staff (without research duties)	6	8
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)		
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)		1
N6: Other contractual staff (without research duties)	1	1
TOTAL N1 to N6	14	17



Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	4	
Theses defended	5	
Postdoctoral students having spent at least 12 months in the unit*		
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	7	

2 • General assessment of the unit

The unit « Pathophysiology and Clinical Pharmacology of Pain » conducts a highly original work, rooted in excellent basic science translated to clinical pain conditions of significance relevance. The quality and impact of the work are strong. In the 10 past years, the team has demonstrated rapid translation of research into clinical output, with excellent and integrated clinical links and collaborations. This has allowed them to launch an epidemiological line of research on chronic pain that was previously lacking in France.

The unit shows an excellent track-record of high quality, high impact studies; it has published 86 peer-reviewed papers in the past 5 years in Pain, Brain, Ann Neurol., Anesthesiology, J Neurol Neurosurg Psychiatry, Gut, etc, with average IF=5. From 2000 to this date, 15 of their papers have been cited more than 100 times, reflecting the value the community places on their work. More than 120 invitations to lecture have been honoured at international meetings during 2008-2013.

Quality and stability of partnerships are excellent, particularly the clinical collaborations with an impressive numbers of hospitals. One specific feature of the team is indeed to function rather as a network than a 'unit', in the sense that most of the research work is distributed among a number of university hospitals within the Paris area. This is related to their transverse approach involving several medical disciplines and the lack of on-site research facilities (e.g. neuroimaging, neurophysiology). This cannot be seen as a drawback, as it has fostered the development of a large network of collaborations in response to specific needs (e.g. fMRI, evoked potentials recordings, skin biopsies). The good synergy between members working in different hospitals provides a unique opportunity for rapid translation of research into clinically relevant data.

The capacity to raise funds is very high, and more than 70 % of total funding comes from external sources, including 1 national PHRC, and grants from public organisms (Ministry of Health) and private research foundations (APICIL, CNP, UPSA, Fondation de France).

Institutional support is also very strong from both the Inserm and the university. Translational pain research is indeed detected as a leading theme by the Inserm, and is part of its strategic plan for the following years. University backing is very sound, and the university policy plans in following years will stress the fields of epidemiology and 'handicap', the team being a prominent example of both. Even if the functioning mode of the unit privileges networking to local functioning, stronger local support from the Ambroise Paré hospital would be expected given the quality of the work being done, the unit focus on clinical research and the involvement of several members in the hospital pain clinic.

Nine (9) PhD theses have been started during the past 5 years, and the laboratory is recognised by the PhD students as an excellent training environment. One foreign PhD prepared and defended his thesis in the lab; most ongoing PhDs are medical doctors with a parallel hospital career. Apparently no postdocs have been received in the last term. International presence of post-docs and students is very limited despite the potential attractiveness of the group. Increasing recruitment from abroad should be encouraged.

In summary, this is a highly dynamic team with very strong leadership and management. There is a clear strategy with identifiable goals, and nice cohesion between members despite geographical dispersion. Long-term security for this team and area of research seems guaranteed both by intrinsic quality of the work and institutional



support. The experts committee recommends increasing the number of junior permanent members with skills in the methodological/analysis domains, as there is a need to complement the work of MDs and provide support to them.

The project proposed is innovative, ambitious and likely to produce original results of considerable potential impact. The experts committee detects a possible dispersion of objectives to the next 5-year term, and suggests focusing on those with maximal translational potential and impact in the pain community. Privileging projects with strong transversal interactions and pathophysiological insights over those essentially correlational in nature, or with only tiny relations with the main objectives, may be the price to ensure a convergent and in-depth analysis of the multiple research lines proposed.

Conclusion

An excellent group performing innovative top-level research.

- **Strengths and opportunities:**

High-quality work spanning from pathophysiology to epidemiological studies and clinical trials. Undisputable reputation of team members fostering international contacts and external funding. Past track of most relevant results and influential publications.

- **Weaknesses and threats:**

Possible excessive dispersion of new projects, threatening in-depth analysis and transversality.

- **Recommendations:**

Continue doing top-quality work. Focus research to ensure in-depth analysis of projects and privilege pathophysiologically-oriented over correlational studies. Increase effort to transmit results through generalistic neuroscience journals. Increase number of foreign PhD or post-doc.



3 • Detailed assessments

Assessment of scientific quality and outputs

The scientific quality of past work and project is excellent to outstanding. The two leader senior members are present in the "top scientists" Web-of-Science report, with high citation (H) indexes of 43 and 39. The scientific output in terms of international publications is impressive: 86 peer-reviewed papers were produced in the last 5 years, with average IF= 5.009, of which 69 % were lead by members of the team as first or last authors. Clinical trials and epidemiological tools developed by the unit have had significant impact to orient clinical practice in France and abroad, and two screening questionnaires validated by the unit (DN4 and NPSI) have been translated to more than 50 languages. Most of the team's scientific output is published in good international journals with emphasis of pain (50 % of the production goes to pain-related journals). Although pain journals are a logical output for the team's work, the overall quality of the studies would deserve effort to publish in generalistic neuroscience journals, the presence of which in the list is relatively limited.

Assessment of the unit's academic reputation and appeal

The unit has a high academic reputation. The senior members of the team are regularly invited to lecture at international meetings and conferences, and sum up more than 120 oral presentations as invited speakers in the last 5 years. In parallel, a number of members participate to national and international teaching courses, symposia and/or workshops, and have organized/chaired personally such events in several occasions. Members have been appointed to the boards of international journals (Pain, European Journal of Pain), participate in ongoing European networks (PainOut, NeuroPain, euCPSP) and collaborate or coordinate international guidelines/recommendations for the assessment and therapy of pain (NeupSIG and EFNS Guidelines for neuropathic pain assessment, QST use and pharmacological therapy). The head of the unit is president-elect of the French Society for pain research (SFETD). Ability to rise external, competitive funding (independent from recurrent institutional support) is high, with more than 70% of funding coming from external sources. Despite the scientific appeal of the group, international presence of post-docs and students is limited, and increasing recruitment from abroad should be encouraged. One high-standard researcher working in US is planning to join the group during the next term.

Assessment of the unit's interaction with the social, economic and cultural environment

The interactions with the economic and social environment are excellent. Partnerships are multiple and stable. Industrial collaboration is outstanding, with more than 15 contracts with private partners, and steady consultancy of senior members with pharmaceutical companies for the development of new drugs. Major interactions with patients' organizations (syringomyelia, fibromyalgia, glossodynia, irritable bowel syndrome) which in turn support the unit's multiple clinical trials and epidemiological studies. Senior members regularly participate in general audience-oriented activities via general press or television programs, and the unit is present in public awareness campaigns such as the "semaine du cerveau", "Universcience" or "Bar des Sciences" organized by CNRS and INSERM.

Assessment of the unit's organisation and life

There is a strong coherence of the group, based on a network-oriented organisation. Studying pain of multiple clinical origins has prompted a transverse approach with members working in different hospitals and disciplines. Despite the spatial segregation and different workplaces within Paris, the team exhibits a very neat integration, with fortnightly meetings gathering seniors and juniors, where students are asked to present their ongoing projects, and weekly smaller meetings to discuss specific points. Being active in several hospitals fosters the possibility of recruiting large patients' samples. Three members of the unit have been recently appointed professors or associate professors, and two new doctors have joined the staff (two others are joining the group during the next term). Polyvalent training of research technicians enable them to work with different members of the team, thus enhancing the structure solidity. The discussion of the experts committee with students and technicians at the end of the visit confirmed the above impression of coherence and commitment.



Assessment of the unit's involvement in training through research

The unit has extensive participation in training, both academic and through research. Since its creation, it has been affiliated to the Doctoral School "ED 158 cerveau-cognition-comportement" in Université Paris 6, and within this frame 9 students have prepared their PhD (5 of them already defended). Senior members participate in different pain medicine university courses, and have organised numerous international seminars in France ("cours supérieurs" of French Pain Society, Master of pain medicine) and abroad (European Federation of Neurological Societies (EFNS), European federation of pain chapters (EFIC), International Association for the Study of Pain (IASP), European League Against Rheumatism (EULAR). Different members of the team participate, organise or coordinate a number of university diplomas from 3 Paris universities on acute and chronic pain, pharmacological therapy, anaesthesiology and gastroenterology. The academic commitments and multiple competences of the team members (neurology, anaesthesiology, gastroenterology, internal medicine) obviously favours the involvement of the unit in teaching activities, which is outstanding.

Assessment of the strategy and the five-year plan

The research project follows the transversal strategy and is rooted on the dynamics established during the past years. The project is presented in 5 axes, namely:

a) mechanisms and factors predicting hyperalgesia, itself containing 3 sub-axes: postoperative hyperalgesia after autograft iliac crest bone harvest, diffuse hyperalgesia after aromatase inhibitor treatment, and role of gut microbiota in intestinal hyperalgesia;

b) new treatment strategies (repetitive cortical stimulation and botulinum toxin);

c) cognitive functions and chronic pain;

d) application of network meta-analysis to clinical trials. The oral presentation included a further axis;

e) based on the application of the 'thermal grill hyperalgesia' to patients with either neuropathic or dysfunctional pain.

Each of these research areas are intrinsically interesting, and served by competent researchers; in each of them a senior and a junior ensure the coordination. There appears to be a thematic dispersion as compared with previous activities of the team; while some projects remain strongly interconnected, and rooted in pathophysiological hypothesis testing, others may lack strong transversal interactions (e.g. the study of gut microbiota) or are more correlational than pathophysiological (e.g. cognitive function correlates of chronic pain). Although each project has its intrinsic qualities, one may wonder whether such thematic dispersion might be detrimental to a convergent and in-depth analysis of multiple and somewhat unconnected results.



4 • Conduct of the visit

Visit date:

Start: Monday, 20 January 2014 at 08.45 am

End: Monday, 20 January 2014 at 05.00 pm

Visit site: Centre d'évaluation et de traitement de la douleur

Institution: Hôpital Ambroise Paré

Address: 9 Avenue Général De Gaulle, 92100 Boulogne-Billancourt

Specific premises visited: Centre d'évaluation et traitement de la douleur

Conduct or programme of visit:

08.45 am	Welcome breakfast
09.00 am	Closed door meeting (AERES Scientific Delegate (DS) + experts committee
09.15 am	Presentation of the experts committee and of AERES to the unit by the DS
09.30-10.30 am	The director of the unit Mr Didier BOUHASSIRA presented the overall past activities in the 2008-2013 period and summarized the main lines of the project
10.30-01.10 pm	(with coffee break between 11.10-11.30 am). Team leaders presented each axis of the project. The general structure was "one junior + one senior presenters" (presentation + questions). Themes were: <ul style="list-style-type: none"> - new treatment strategies: Mr Xavier MOISSET and Ms Nadine ATTAL - postoperative pain: Ms Valeria MARTINEZ and Mr Dominique FLETCHER - visceral pain: Mr Henri DUBOC and Mr Jean-Marc SABATÉ - musculoskeletal pain: Ms Françoise LAROCHE and Mr Serge PERROT - cognition and pain: Ms Anne DUBOIS-MASSÉLIN and Ms Sophie BAUDIC - experimental pain: Mr Pascal ALFONSI and Mr Didier BOUHASSIRA
12.50 pm	Lunch with all laboratory staff ("buffet" on site)
02.00-02.30 pm	Meeting of members of the experts committee & DS with the representatives of Inserm, Université de Versailles and the UVSQ 'École Doctorale'
02.30-02.50 pm	Meeting with PhD students and fixed-term contract researchers
02.50-03.15 pm	Meeting with the technical staff
03.15-03.45 pm	Closed door meeting (members of the experts committee and DS)
03.45-04.15 pm	Discussion with the head of the unit



5 • Supervising bodies general comments



UNIVERSITE VERSAILLES SAINT-QUENTIN-EN-YVELINES

UMR U987

Laboratoire de Physiopathologie
et Pharmacologie Clinique
de la Douleur

March 17, 2014

Responses to the visiting committee

S2PUR150008315-PHYSIOPATHOLOGIE ET PHARMACOLOGIE CLINIQUE DE LA
DOULEUR – 0781944P

We thank the members of the committee for their comments and constructive
suggestions.

Sincerely,

Dr. Didier BOUHASSIRA
Head of the "Pathophysiology and Clinical Pharmacology
of Pain" INSERM 987 Unit

"



Versailles, le mercredi 19 mars 2014

Le président de l'Université de Versailles
Saint-Quentin-en-Yvelines

à

Dossier suivi par :
Christian Delporte,
Vice-Président du conseil scientifique chargé de la
recherche et du développement scientifique
Réf : JLV/CD/MC/DREDVal 14-098

Monsieur Didier Houssin
Président
Agence dévaluation de la Recherche et de
l'enseignement supérieur
20 rue Vivienne - 75002 PARIS

**Réf. : S2PUR150008315 - PHYSIOPATHOLOGIE ET PHARMACOLOGIE CLINIQUE DE LA
DOULEUR - 0781944P**

Objet : Evaluation des unités de recherche : Volet Observations de portée générale

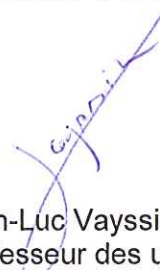
Monsieur le Président,

Nous avons pris connaissance avec le plus grand intérêt du rapport de l'AERES concernant la demande de renouvellement de l'Unité Mixte de Recherche, actuellement UMR 987, dénommée **S2PUR150008315 - PHYSIOPATHOLOGIE ET PHARMACOLOGIE CLINIQUE DE LA DOULEUR - 0781944P**», portée par M. Didier Bouhassira.

Nous remercions l'AERES et le comité pour l'efficacité et la qualité de leur travail d'analyse et nous nous félicitons de cette évaluation. Le directeur d'unité et ses équipes ne manqueront pas de mettre en œuvre les recommandations constructives émises dans ce rapport avec le soutien de ses tutelles pour la période 2015-2019.

Nous vous adressons ci-joint la réponse du porteur de ce projet formulée au regard du rapport de l'AERES.

Nous vous prions de croire, Monsieur le Président, à l'expression de nos cordiales salutations.


Jean-Luc Vayssière
Professeur des universités

