Variabilité de réponse aux psychotropes

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Variability of the response to psychotropic drugs

VariaPsy

Under the supervision of the following institutions and research bodies:

Université Paris Descartes

Université Paris 7 – Denis Diderot

Institut national de la santé et de la recherche médicale

February 2013

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

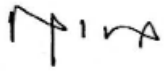
Research Units Department

President of AERES

Didier Houssin

Research Units Department

Department Head



Pierre Glaudes

The president of AERES "signs[...], the evaluation reports, [...]countersigned for each evaluation department by the relevant head of department (Article 9, paragraph 3, of french decree n°2006-1334 dated 3 november 2006, revised).

Grading

Once the visits for the 2012-2013 evaluation campaign had been completed, the chairpersons of the expert committees, who met per disciplinary group, proceeded to attribute a score to the research units in their group (and, when necessary, for these units' in-house teams).

This score (A+, A, B, C) concerned each of the six criteria defined by the AERES and was given along with an overall assessment. NN (not-scored) attached to a criteria indicate that this one was not applicable to the particular case of this research unit or this team.

Criterion 1 - C1: Scientific outputs and quality;
Criterion 2 - C2: Academic reputation and appeal;
Criterion 3 - C3: Interactions with the social, economic and cultural environment;
Criterion 4 - C4: Organisation and life of the institution (or of the team);
Criterion 5 - C5: Involvement in training through research;
Criterion 6 - C6: Strategy and five-year plan.

With respect to this score, the research unit concerned by this report and its in-house teams received the overall assessment and the following grades:

- Grading table of the unit: Variability of the response to psychotropic drugs

C1	C2	C3	C4	C5	C6
A	A	A	A	A	A

- Grading table of the team: Biomarkers of relapse and therapeutic response in addiction and mood disorders

C1	C2	C3	C4	C5	C6
A	A	A	NN	A	A

- Grading table of the team: Mechanisms of toxicity and therapeutic optimization of psychotropic drugs

C1	C2	C3	C4	C5	C6
A	A	A	NN	A	B

- Grading table of the team: Pathophysiology and therapeutic targets of the blood-brain barrier

C1	C2	C3	C4	C5	C6
A	A+	A	NN	A	A

Evaluation report

Unit name:	Variability of the response to psychotropic drugs
Unit acronym:	VariaPsy
Label requested:	Inserm, University Paris Descartes, University Paris Diderot
Present no.:	Inserm U.705, UMR CNRS 8206, University Paris Descartes, University Paris Diderot
Name of Director (2012-2013):	Mr Jean-Michel SCHERRMANN
Name of Project Leader (2014-2018):	Mr Jean-Louis LAPLANCHE

Expert committee members

Chair:	Mr William COUET, Université de Poitiers
Experts:	Mr Bruno AOUIZERATE, Université Bordeaux Segalen
	Mr Jean-Michel AUBRY, Université de Genève, Suisse
	Mr Hot BUN, Faculté de Pharmacie de Marseille (representative of CNU)
	Mr Mark GUMBLETON, Cardiff University, UK
	Mr Pierre MARQUET, Université de Limoges (representative of CSS 8 Inserm)
	Mr Marcello SOLINAS, Université de Poitiers
	Mr Paul VERBRANCK, Université libre de Bruxelles, Belgique

Scientific delegate representing the AERES:

Mr Yves TROTTER

Representative(s) of the unit's supervising institutions and bodies:

Ms Christine CLERICI, Université Paris Diderot

Mr Jacques GRASSI, Inserm

Mr Stefano MARULLO, Université Paris Descartes

1 • Introduction

History and geographical location of the unit:

The unit "Variability of the response to psychotropic drugs" for 2014-2018 is a substantial reconstruction of the former unit Neuropsychopharmacology of addictions: experimental and clinical variability and vulnerability (UMR INSERM U705, CNRS 8206, Paris Descartes and Paris Diderot Universities) created on January 1st, 2005 and renewed in 2010 under the direction of Prof. Jean-Michel SCHERRMANN. The unit is located at the Faculty of Pharmacy at the Paris Descartes University.

Management team:

Mr Jean-Louis LAPLANCHE (Head of the unit)

Mr Frank BELLIVIER (Head of team 1)

Mr Bruno MÉGARBANE (Head of team 2)

Mr Xavier DECLÈVES (Head of team 3)

AERES nomenclature:

SVE_L54

Unit workforce:

Unit workforce	**Number as at 30/06/2012**	**Number as at 01/01/2014**	2014-2018 **Number of project producers**
N1: Permanent professors and similar positions	25	23	23
N2: Permanent researchers from Institutions and similar positions	3	1	1
N3: Other permanent staff (without research duties)	17	16	
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)			
TOTAL N1 to N6	46	40	24

Percentage of producers	***100 %***

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	8	
Theses defended	14	
Postdoctoral students having spent at least 12 months in the unit*	1	
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	12	12

2 • Assessment of the unit

Strengths and opportunities:

- Experienced leader who succeeded in defining a scientifically coherent project for the three new teams after profound reorganization of the unit;
- Probably the only group worldwide connecting blood brain barrier and response to psychotropic drugs;
- High translational potential with unique cohorts of patients build over the last years;
- Opportunities of merging human and material resources from two Universities (Paris 5 and Paris 7) engaged in a network for integrated research;
- Strong local support with major improvements of lab facilities approved for the short term.

Weaknesses and threats:

- Too much effort dispersion, especially since clinical projects are sometimes very ambitious;
- Lack of permanent staff for appropriate data management and good clinical practice observance;
- No administrative staff;
- Lack of strategy to conduct the scientific project over the next five years and possibly beyond.

Recommendations:

- Concentrate resources on the most relevant clinical projects;
- Continue to strengthen the translational approaches.

3 • Detailed assessments

Assessment of scientific quality and outputs:

During the period (2007-2012) the unit was entitled "Neuropsychopharmacology of addictions: experimental and clinical variability and vulnerability" and comprised three teams whose research activities spanned basic through translational to clinical investigations conducted by researchers with appropriately balanced expertise. The central theme of the research is the identification of neurobiological, pharmacokinetic and pharmacogenetic factors that determine addictive behaviours. A clear intent of the group is that experimental laboratory-based studies are driven by clinical problems.

The unit as a whole published 207 international level publications across the three teams, involving 17-20 PI/CI (Prof/Assist Prof.). Some 29 research articles resulted from collaborations across teams within the unit. The unit publication rate represents a productivity of approx 12 papers per Prof/Assist Prof. over the six-year period. Team 2 delivered 65 of these publications with a productivity at 16 papers per Prof. /Assist Prof. over the same period. The report indicates the unit's performance as a whole to be satisfactory. This is a fair assessment but with Team 2 performing relatively stronger, at least in terms of volume, and at a level (at least with respect to volume) regarded as consistent with an internationally competitive research unit.

Assessment of the unit's academic reputation and appeal:

As required for academic reputation, researchers and professors within the unit have contributed, at general and specialised National and International meetings, to the scientific and scholar debate in their subject area. Evidence of some involvement in international research networks is provided in the overall summary.

Although the recruitment of international researchers, honours/awards etc… is not at a level expected from an internationally leading group, the unit has real International / National outlook with collaborations abroad including with Japan.

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

The unit as a whole conducts translational research from basic science to patient care. It has connections with the pharmaceutical sector, other national INSERM units and clinical practitioners. Several staff members have served as experts / advisors on professional, regulatory (e.g. EMA) and scientific opinion-leading/policy-forming bodies. Many team members are clinicians and therefore the unit research is influenced by questions or opportunities encountered by clinicians in their daily activity. Yet the team interactions with the social and cultural environment could be improved.

Assessment of the unit's organisation and life:

For the unit as a whole the last years have seen an approximate 36% increase in total funds with independent public contracts being the main growth area and which appears to represent increased income from clinical research contracts. The administrative and financial management for the unit is acknowledged to be complex in part due to the relationships of the unit with its multiple affiliates (INSERM, CNRS, Universities). It is unclear how the total budget for the unit is distributed to the teams and the nature of the decision processes for expenditure on pooled capital items.

The unit's floor space has increased since its inception in 2005 but the conditions appear to have still remained challenging until recently (2012), in particular with respect to allocating space for the potential recruitment of researchers. Access to core facilities at IMTCE (Institut Médicament Toxicologie Chimie Environnement) and the new building (animal facility) at Paris Descartes is noted.

While it is understandable for the purposes of profile that the unit is organized into teams of coherent scientific focus there is a slight question as to whether this has translated into an administrative, budgetary and physical separation of the teams that may actually limit the full potential of the unit's research activities. For example, despite the unit as a whole possessing a focussed scientific aim, and the teams possessing complementary methods and knowledge, only 14% (29/207) of outputs arise from cross-team collaborations. Cross-team collaborations should be more extensive and may allow publications in higher ranked journals.

Assessment of the unit's involvement in training through research:

There is a relative lack of information on the accreditation and governance processes for research training and the outcomes of the students, in particular regarding their progress into research careers.

The report indicates that the unit as a whole hosted 14 PhDs, which over six years is a relatively small number. However, the unit has been more active in the training of Master students (44 over the period), a generallly less critical metric used for assessment of research training. The unit has also hosted foreign students as part of the Erasmus programme. Professors have been highly engaged in teaching activities across clinical and non-clinical backgrounds.

Assessment of the five-year plan and strategy:

The focus for the 5-year programme of the new unit "**Variability of response to psychotropic drugs"** is on the variability of the response to psychotropic clinical agents, as well as to drugs abuse.

The science involves clinical (Teams 1 & 2) through to fundamental (Teams 2 & 3) research approaches. One of the acknowledged strengths of the new programme is the very necessary, improved integration between clinical and non-clinical teams. Yet the mechanisms by which this 'improved integration' is to be achieved are unclear.

For Team 1, and to some extent Team 2, identifying clinically useful predictive biomarkers of patient responsiveness and drug toxicity will be a significant challenge. This will be true not only in defining appropriate endpoint measures but also in identifying the most significant biomarker profile – which will inevitably be a complex of co-variates. Validated and robust biomarker profiles will be the first step toward patient stratification in therapy decisions. This approach is assumed to further result in significant changes in daily physician practice and to substantially improve patient outcomes beyond the classical clinical interventions. However, the contingency plans to mitigate delays in approval of clinical projects will need to be thoroughly tested, and the appointment of a clinical research data base manager prioritorised.

For Team 3 the BBB (Blood Brain Barier) is the focus, in particular with respect to: Theme 1 - unfold the functioning of drug transporters and drug metabolising enzymes in the brain microvascular cells, in the context of the entire neurovascular unit; Theme 2 - understand how the BBB adapts to pathology and also to drug therapy. Overall the projects in Team 3 (notably Theme 2) represent elements of real originality. In parts the challenges of transition to the clinic/patient and/or to the commercial sector have possibly been underestimated or the clinical value of the expected findings overstated. The integration of non-clinical and clinical investigations is appreciated by the committee.

4 • Team-by-team analysis

Team 1 : Biomarkers of relapse and therapeutic response in addiction and mood disorders

Name of team leader: Mr Frank BELLIVIER

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions		5	5
N2: Permanent EPST or EPIC researchers and similar positions		1	
N3: Other permanent staff (without research duties)		7	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)			
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6		13	5

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students		
Theses defended		
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions		4

• Detailed assessments

Assessment of scientific quality and outputs:

Team 1 "Biomarkers of relapse and response to treatments in addictions and mood disorders" succeeds to the previous team 3. The research work was organized according to two major themes: i) "Clinical Addictology, Genetics and Therapeutics", and, ii) "Clinical and Experimental Toxicology of Opiates". Given that Mr Bruno MEGARBANE, who was part of the former team 3 is now taking the leadership of the new team 2 for the next 5-year contract, the scientific quality of the team for the period 2007 - 2012 was therefore evaluated only on the basis of the scientific production of the former leader of the previous Team 3. This production may be qualified as high given the numerous publications (69 original papers), mostly in high-standard clinical journals in Psychiatry (J. Clin. Psychiatry, J. Neuopsychopharmacol., Mol. Psychiatry, but also Trends Genet., Plos One….).

Assessment of the unit's academic reputation and appeal:

The expertise area of the new team leader is mainly dedicated to the study of affective disorders and he seems to have more limited expertise in addiction medicine. Yet the former team leader who is a recognized expert in the clinical management and research in addicted patient, will continue to collaborate with this team. The new team leader is well known as a national and international expert on bipolar disorders. He has conducted relevant clinical studies in this field and is an author or coauthor of numerous papers in major scientific journals. Furthermore he has actively participated in the creation of a national network of expert centers on that topic within the Foundation FundaMental.

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

As already mentioned, the team leader is a well-known expert in the field of bipolar disorders investigations and treatment. He has published in leading journals in this field in collaboration with another productive research team. Noticeably he plays a leading role in networks such as the "centres experts" on bipolar disorders in France, and he also contributes to international networks.

Assessment of the unit's involvement in training through research:

The small number of permanent researchers is a potential weakness of the unit. However, there is quite a large number of clinical researchers who are highly involved and motivated for participating in the clinical research conducted within the team 1. The implication of Master and PhD students appears to be particularly effective in the team, as well as in the other teams of this research unit.

Assessment of the five-year plan and strategy:

The 5-year project is oriented towards the identification of biomarkers that are able to predict the risk of relapse and toward the variability of therapeutic responses in either addiction or mood disorders. Several biochemical, genetic or brain imaging characteristics, which are assumed to have strong relationships with either addiction or bipolar disorders, will be examined using various, appropriate, and complementary experimental tools. The development of psychiatric cohorts will be favored by the intervention of the team leader within the national network of expert centers on bipolar disorders of the Foundation FundaMental. Additionally, the Hospital department of Adult Psychiatry directed by the team leader is highly specialized in the clinical management of addicted patients, who will be easily recruited for the research programs defined in the scientific project. The confrontation and the integration of putative biomarkers in the complexity of clinical situations remain to be taken into consideration. However, the number of projects considered across the different axes of research is probably too high, making the present program relatively complex to develop over the limited period of the next 5 years.

Conclusion:

● Strengths and opportunities:

This team will be able to rely on unique and invaluable cohorts of patients built over the last years to address medically important issues.

It has access to various sophisticated, complementary and pertinent methodologies, from molecular biology to brain imaging.

● Weaknesses and threats:

Multiple co-variates will make it very difficult to identify clinically useful predictive biomarkers of therapeutic responsiveness in psychiatric patients.

The lack of a database manager in the unit and the potential significant delays in obtaining clinical trial approvals.

By dispersing on too many projects, there is a risk that the team reduces its ability to produce highly relevant publications and to compete at the international level.

● Recommendations:

It can be recommended that the team re-focusses its research on a more limited number of projects. At least, the research efforts on the scientific projects that are more likely to establish the team as an international reference in the field should be prioritized.

Team 2 : Mechanisms of toxicity and therapeutic optimization of psychotropic drugs

Name of team leader: Mr Bruno MEGARBANE

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions		8	8
N2: Permanent EPST or EPIC researchers and similar positions			
N3: Other permanent staff (without research duties)		4	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)			
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6		12	8

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students		
Theses defended		
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions		5

• Detailed assessments

Assessment of scientific quality and outputs:

The team has a consistent track record of publications in journals that are well established and respected in the domain (Clin Toxicol, Toxycology, Toxicol Rev., Mol Pharm.). Although not directly linked with its main research topic, the team has some publications in high impact journals resulting from collaborative research projects (ann Intern Med, Gut, Crit care.).

Assessment of the unit's academic reputation and appeal:

The team has not organized meetings or symposia during the previous contract and has not been able to attract foreign PhD or post-doc students. Yet it has international visibility, as demonstrated by the frequent invitations of the team leader to give seminars abroad and in international events. It also benefits from collaborations at the national and international levels that demonstrate international recognition and will strengthen the team's research projects.

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

The team interactions with the social and cultural environment are scarce. Yet this team is mostly a clinical team with a strong link between basic research, clinical research and patient care. Therefore several aspects of clinical pharmacology-toxicology of the team research appear to be highly influenced by questions or opportunities encountered by clinicians in their daily activity. The medical aspect of the research performed by the team is thus evident and in line with the profiles of professors in the team. It will be important for the team to demonstrate that these interactions are bidirectional and that their research findings are also able to influence clinical practices.

Assessment of the unit's involvement in training through research:

The team is mostly composed of professors with several responsibilities in the master programs of the 2 universities to which they belong. In addition, an important number of master and PhD students are trained in the unit. Students have different backgrounds including medicine, pharmacy and biology, which enrich the environment in the laboratory.

Assessment of the five-year plan and strategy:

The research project of team 2 has 3 main themes with each theme further divided in several focus of research. These focus of research cover a wide range of aspects of clinical pharmacology-toxicology that are undoubtedly of interest. However, some projects appear to be partially unrelated between them and/or not in line with the unit thematic. For instance, project 1.2 and most of theme 3 appear to be marginal and may be dropped from the research activity or performed in collaboration with National or International partners in order to increase the impact of the research. Given the size of the team, the absence of full-time researchers and the presence of many teaching researchers with important clinical duties, dispersing and diluting the energy and budget on too many projects is a risk. Theme 1 appears as really promising. Project 1.1 on buprenorphine is the one where the team has a solid experience and the highest visibility in terms of publications and citations. It is in tight relation with the clinical activity of the team members and it represents an interesting avenue for research and should have important applications.

Conclusion:

● Strengths and opportunities:

This teams has a solid background in clinical pharmacology and toxicology and has been able to address several research aspects that are relevant to clinical practice and are relatively unexplored.

It has the opportunity to strenghten its position in some of these domains, as well as to develop some new lines of research that may position them as leaders in France and a reference for partners at the European and extra-european levels.

The team has produced major efforts in developing projects in collaborations with team 1 and 3.

● Weaknesses and threats:

The team appears to have a tendency to spread its research efforts on many projects, some of which are in part unrelated to the main research thematic of the team and even, in a few instances, probably beyond the skills of the team members. By dispersing on too many projects the team risks to reduce its ability to produce high level publications and to compete at the international level.

● Recommendations:

The committee recommends that the team focuses on a more limited number of projects and go deeper into them (vertical research), in order to be able to be competitive at the international level.

Team 3 : Pathophysiology and therapeutic targets of the blood-brain barrier

Name of team leader: Mr Xavier DECLEVES

Workforce

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions		10	10
N2: Permanent EPST or EPIC researchers and similar positions			
N3: Other permanent staff (without research duties)		4	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)			
N6: Other contractual staff (without research duties)		1	
TOTAL N1 to N6		15	10

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students		
Theses defended		
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions		3

• Detailed assessments

Assessment of scientific quality and outputs:

This Team (ex-team 2) has published 65 papers with a productivity at 16 papers per Prof. /Assist Prof. over the 6-year period.

It performed relatively stronger than the other two teams, at a level (at least with respect to volume) regarded as consistent with an internationally competitive research unit.

The scope of research of this team is represented through two overlapping (significantly so in terms of intellectual framework and methodological bases) cross-cutting themes. It has exploited a broad range of methodological approaches from, for example, cell/molecular biology, to studies with intact human and animal tissue, physiologically-based pharmacokinetic modelling, or studies using in-vivo models (collaboration with other Teams) and imaging (PET, SPECT). Importantly, its research can mainly be seen as driven by clinical problems or needs.

Key discoveries of ex-team 2 during the period, as identified in the scientific report, include:

- Theme 1 - revealed the differential expression of cytochrome P450s and ABC drug transporters in human fresh brain microvessels. This is quite original with respect to the tissue source used (human brain capillaries – fresh) and is revealing significant new data useful to both the academic and research user communities, e.g. the pharmaceutical sector. It revealed the shortcomings of some more commonly used in-vitro systems. Some of these works have generated new hypotheses and should be highly cited (in particular references 1, 2 page 37). The mechanistic work on transporters and metabolism at the BBB is appropriately supported by more readily used cell line investigations. The papers (1, 2 page 37) about the human fresh brain microvessel research are in medium ranking, but sound journals (IF 4-5) in neuroscience and molecular pharmacology -(J. Cerebral. Blood flow & Metab., AAPS J.) The papers (3, 4 page 37) about transporters in human cells lines and reporting physiologic PK modelling in rat in-vivo are in decent journals within the more applied pharmaceutical area (IF 3 - 4.7).
- Themes 1 and 2 - demonstrated that the cerebral toxicity / adverse events of opioids such as morphine, methadone and nor/buprenorphine, can be modulated, at least to some extent, by the activity of ABC transporters, whose expression in turn can be modulated by the opioid drugs and their withdrawal. This research is driven by clinical observations and provides some mechanistic understanding. The papers issued from this research (6,7,12,13 page 37) are again in medium ranking, well respected journals (IF 4 - 6) and are reaching the appropriate target readership (Mol. Pharm., J. Alzheimzer Dis.).
- Theme 1 - led to the discovery of a new active influx transporter capable of transferring a selected number of amine-containing psychoactive substances (including nicotine and cocaine) across the blood brain barrier. The molecular identity of this transporter is still to be revealed. At the time of the scientific report, a single paper (reference 8 page 37) had been published on these results, however in an appropriate and well recognized neuroscience journal (IF 5) (Fluids Barriers CNS).

Overall the journals in which this Team publishes its research are of middle-ranking quality based on their IF, but benefit from international recognition and appropriately capture the key readership for the team research. The team is pursuing work involving investigations from molecular to systems biology and with clinical significance, and as such it has the capacity to be competitive for higher ranked journals. However, it must be reiterated that blood-brain barrier research is a relatively small community, (compared to neuroscience) and as such, the journal IF means very little in terms of work recognition by the peer community.

There is an appropriate distribution of senior authorship across the 65 peer-reviewed publications. More junior professors recruited during the period have made scientific contributions through peer-reviewed research publications.

Assessment of the unit's academic reputation and appeal:

As required for academic reputation, professors within this team contribute to the scientific and scholar debate in their subject area at general and specialised National and International meetings. Such contributions include a range of invited international conference, by a senior member of the team and oral and poster communications by other persons. A senior member has also made scholar contributions through book chapters. Team members serve as journal Editors (Eur J. Drug Metab. Pharmacokin.) and on Editorial boards. However, across the team as a whole the level of such contributions would fall relatively short of the highest level of International competitiveness.

Involvement of this team in the international research networks is not apparent. Yet it is involved in the organisation of annual National meetings on ABC transporters in conjunction with Belgium.

The unit has some International / National outlook with collaborations with Japan, with the Pharmaceutical sector and other national INSERM units.

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

The research of this team is best defined as basic to early translational, with benefits for the clinical practitioner, for the patient and for the commercial sector somewhat downstream. This output remains to be established in the future. Nevertheless, interactions exist with research users, in particular the pharmaceutical sector and clinical practitioners.

Team members have served as experts / advisors on professional, regulatory (e.g. EMA) and scientific opinion-leading/policy-forming bodies. They are also engaged in the public communication of science. These activities are however at a level that would not be considered extraordinary.

Assessment of the unit's involvement in training through research:

This Team has contributed significantly to the hosting of all the unit's PhDs over the last six years and has been active in the training of Master students. The team has hosted foreign students as part of the Erasmus programme. The team members are heavily engaged and quite successful in both research and teaching activities.

Assessment of the five-year plan and strategy:

The 5-year programme aims at investigating the factors of variability of the response to psychotropic therapeutic agents as well as drugs of abuse.

The BBB is the focus of the team research, in particular to: investigate the functioning of drug transporters and drug metabolising enzymes in the brain microvascular cells in the context of the entire neurovascular unit (Theme 1); and to study how the BBB adapts to pathology and also to drug therapy (Theme 2). Overall, the projects of Team 3 present elements of real originality. The challenges linked to the potential translation of this research to the clinic/patient and/or to the commercial sector have been under-estimated, and/or its clinical value overstated. However, the integration of non-clinical and clinical investigations is appreciated by the visiting committee.

Theme 1

(i) **Novel transporter in BBB for psychotropic drugs**: - Whether this is a completely new SLC transporter remains to be determined. However, the study of its expression and functionality at the BBB represents a continuation of the 2007-2014 programme. Issues to consider are the extrapolation of functional data from animals to the humans, the possibility to crystallize the transporter to decipher its structure and permit molecular modelling and inhibitor drug design, and the capacity to undertake drug design and synthesis that will lead to intellectual property (IP). Access to immune-electron-microscopy might be appropriate to ultimately delineate transporter expression at the luminal versus abluminal surfaces.

(ii) **Characterisation of Li transport**: - This may be an important clinical question, with science ultimately influencing therapeutic decisions. However, from an academic perspective the publications arising from the in-vitro work alone may not be highly cited and it will be essential to fully integrate the in-vitro and clinical elements of the research.

(iii) **Characterisation of ABC transporters**: - Represents a continuation of work from the 2007-2014 programme. Two elements that are **quite original** are the investigations of the endogenous substrates and the impact of transporters upon the broader native functionality of the BBB.

Theme 2

These projects are more basic in nature and address how mediators can affect native functionality of the BBB and offer significant potential for new discoveries.

(i) Modulation of BBB upon chronic opioïd exposure and withdrawal

(ii) **Mechanisms of modulation of CYP1B1/AhR in the BBB**

(iii) **Dynamics and heterogeneity of brain endothelium** – this in particular is very original.

An area for growth in the team might well be study of the mechanisms involved in transcytosis across the BBB. This is captured to some extent within Theme 1 as part of drug targeting strategies. The model systems available within the unit should help this particular topic to rapidly mature and the pharmaceutical industry is particularly interested in this for the delivery of biological agents to the CNS. This may also be the major focus of the team's 'Vector Brain' project.

Conclusion:

- Strengths and opportunities:

With the former team leader, who was also the unit director, this team has had a central position in the whole unit, and it is supposed to keep playing a leading role in the future, bringing fundamental science to clinical research and making a link with and between the other two Teams.

The new team leader has had very close scientific relationships with the past leader for a sufficiently long period of time to insure the continuity and stability required after the profound unit reorganization.

High translational potential.

Very original and still fully relevant positioning that considerably strengthen the whole project.

- Weaknesses and threats:

The team addresses many questions at once. Thanks to this high diversification the team is unlikely to fail in a competitive and somewhat risky area of research. Yet, it may then be difficult for the unit to be recognized as a top leading group at the international level without more focused research.

- Recommendations:

This team has found a very unique position working on a scientifically relevant project with high translational potential. The team leader should therefore concentrate efforts and resources on linking the basic cellular science to clinical research findings.

5 • Conduct of the visit

Visit date:

Start: Monday 04 february 2013 at 8h30

End: Monday 04 february 2013 at 18h30

Visit site: Faculté de Pharmacie

Institution: Paris Descartes University, Paris Diderot University and Inserm

Address: 4, avenue de l'observatoire, 75006 Paris

Conduct or programme of visit:

8:30 to 9:00 am	Door-closed meeting - Committee members and AERES representative
9:00 to 9:15 am	Introduction of the visiting Committee by the AERES representative
9:15 to 10:00 am	Scientific assessment and projects of the unit (Mr Jean-Louis LAPLANCHE)
10:00 to 10:45 am	Scientific assessment and projects of Team 1 (Mr Frank BELLIVIER)
10:45 to 11:00 am	Pause
11:00 to 11:45 am	Scientific assessment and projects of Team 2 (Mr Bruno MÉGARBANE)
11:45 to 12:30 pm	Scientific assessment and projects of Team 3 (Mr Xavier DECLÈVES)
12:45 to 14:00 pm	Lunch and posters
14:00 to 14:45 pm	Meeting with the technical staff (committee members, AERES representative, no head/team leader of the unit)
	Meeting with PhD students and Post-docs and/or fixed-term contract researcher, engineers (committee members, AERES representative, no head/team leader of the unit)
	Meeting with researchers, teaching- researchers (committee members, AERES representative, no head/team leader of the unit)
14:45 to 15:00 pm	Pause
15:00 to 15:45 pm	Meeting with the representatives of the institutions
15:45 to 16:15 pm	Meeting with the head of the UMR
16:30 to 18:30 pm	Door-closed Committee

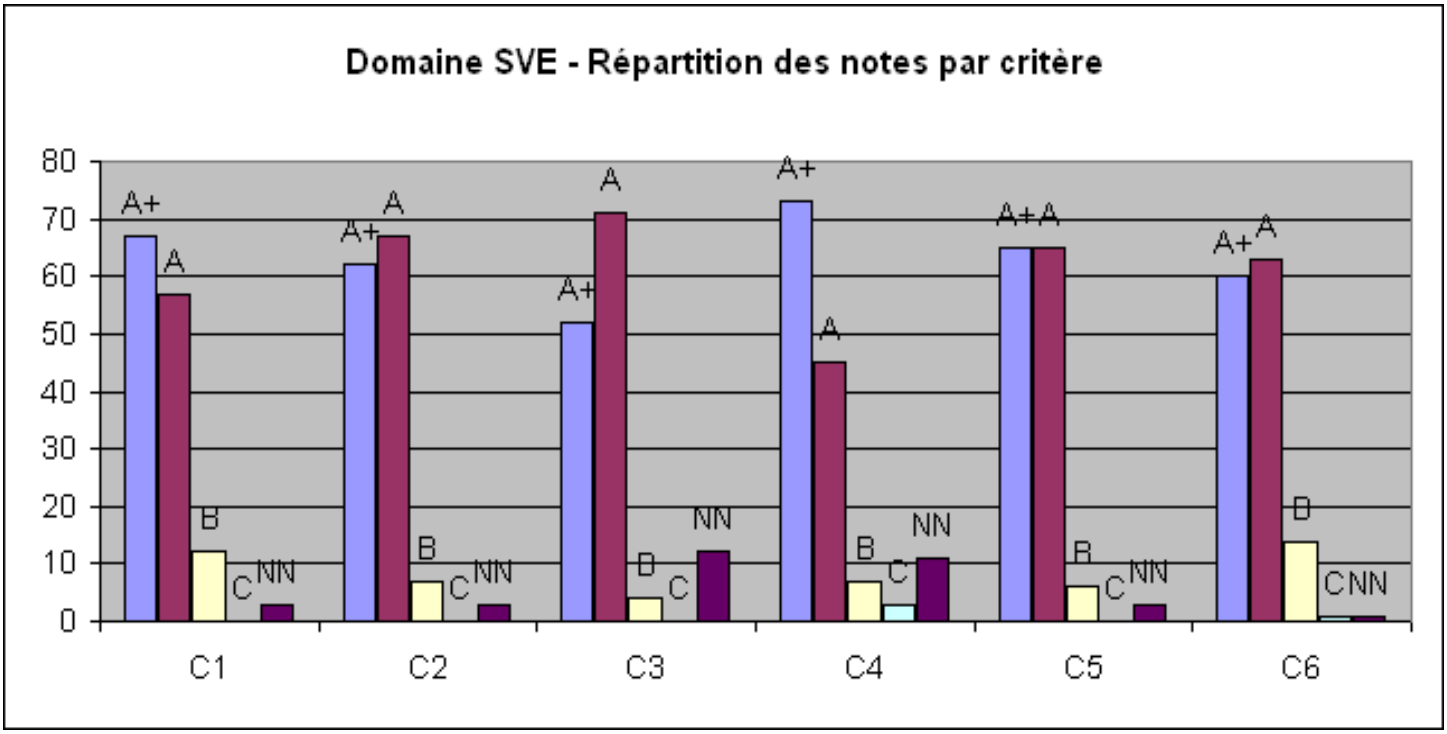
6 • Statistiques par domaine : SVE au 10/06/2013

Notes

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	67	62	52	73	65	60
A	57	67	71	45	65	63
B	12	7	4	7	6	14
C	0	0	0	3	0	1
Non Noté	3	3	12	11	3	1

Pourcentages

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	48%	45%	37%	53%	47%	43%
A	41%	48%	51%	32%	47%	45%
B	9%	5%	3%	5%	4%	10%
C	0%	0%	0%	2%	0%	1%
Non Noté	2%	2%	9%	8%	2%	1%



7 • Supervising bodies' general comments

UNIVERSITÉ PARIS DESCARTES

Vice Président du Conseil Scientifique

Paris le 09.04.2013

Vos ref : S2PUR140006216 –
Variabilité de réponse aux
psychotropes- 0751721N

Monsieur Pierre GLAUDES
Directeur de la section des unités de recherche
Agence d'Evaluation de la Recherche et de
l'Enseignement Supérieur
20, rue Vivienne
75002 PARIS

Monsieur le Directeur

Je vous adresse mes remerciements pour la qualité du rapport d'évaluation fourni à l'issue de la visite du comité d'expertise concernant l'unité « Variabilité de Réponse aux Psychotropes »

Vous trouverez ci-joint les réponses du Directeur de l'unité, Jean-Louis LAPLANCHE, auxquelles le Président et moi-même n'avons aucune remarque particulière à apporter.

Je vous prie d'agréer, Monsieur le Directeur, l'expression de ma considération distinguée.

Le Vice Président du Conseil Scientifique

Stefano Marullo, DM, DesSci

Université Paris Descartes, Vice-présidence du conseil scientifique, 12 rue de l'école de médecine, 75170 PARIS cedex 06
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Inserm U.705 ; CNRS UMR 8206
NEUROPSYCHOPHARMACOLOGIE DES ADDICTIONS :
Vulnérabilité et variabilité expérimentale et clinique
Directeur : Professeur Jean-Michel Scherrmann

April 8th, 2013

Responses to the report from the AERES visiting committee

We thank the Visiting Committee for its comments and suggestions, regarding both our scientific background, the new scientific directions of our project on the response variability to psychotropic drugs, and the organization considerations.

We appreciate that the Committee acknowledges our success in defining a scientifically coherent project for the three new teams after a profound reorganization of the unit. We would like to highlight certain issues:

Strategy to conduct the scientific project:

Regarding our strategy to conduct the scientific project over the next years and possibly beyond, a plan strategy, discussed in the unit, including milestones, deliverables, workforce and financial resources, risk estimation and translational potential will structure the frame to establish the prioritization schemes. As advised by the Committee, we are going to re-focus our research according to two criteria, i) projects allowing interactions with the other teams from the unit, ii) projects that are funded. It is clear that we want to give priority to projects with the highest translational potential as, for example, those aiming to identify the cellular and molecular mechanisms potentially modulating the transport of psychotropic drugs across the blood-brain barrier and responsible for their variable therapeutic or toxic effects thoroughly analyzed in parallel in our patient's cohorts (bipolar disorders and substance abusers).

As noted by the Committee, we are aware of the multifactorial aspects of the diseases that we are studying. We believe that the multiple approaches as proposed in the project (molecular, genetic, biochemical, imaging and extensive phenotyping) by team 1, as well as interaction with basic and experimental science developed by Teams 2 and 3 on specific hypotheses, are appropriate strategies to address this complexity and to identify biomarkers of response variability to treatments.

Following the committee's recommendations, Team 2 will focus in deep on its experimental and clinical research projects in the line of the Unit themes and target energy and future financial budgets on research on opioid- (theme 1.2, 1.3 and parts of 3) and lithium-related vulnerability and toxicity (theme 2). To avoid a possible risk of theme dispersion, the two next offered PhD projects by team 2 will be exclusively dedicated to these two themes. As suggested, projects 1.2 (new recreational stimulant drugs) and parts of theme 3 dedicated to the therapeutic optimization of non-opioid analgesics will be limited to the ongoing national/international collaborations. Additionally, experimental investigations of mechanisms of drug toxicity conducted by Team 2 will highly profit from interactions with the social environment (Paris Poison control centre (CAP) and Centre of evaluation and information on drug dependence (CEIP) and ANSM). Based on our researches focused at responding to clinical concerns, the Unit will be able to provide high-quality information regarding drug toxicity useful to physicians and national authorities.

The new context of the Unit investigating drug response variability in different clinical

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situations is a major opportunity for Team 3 to develop translational researches as expected by the Committee. As an example, the quantification of proteins of interest in surgically obtained human blood-brain barrier will allow the development of physiologically-based pharmacokinetic models. If promising candidates emerge, new imaging probes (ex: PET probes) targeting these blood-brain barrier proteins will be designed and validated as relevant theragnostic tools in psychiatric disorders.

Workforce situation:

The Unit will manage its efforts to increase the work force of Team 2 by the recruitment of a new researcher. After post-doc studies in the US in PK/PD modelling, one of our previous PhD student is now back into Team 2, with a perspective of recruitment as full researcher within the two next years to strengthen our experimental research capacities.

We thank the Committee for the positive feedback he provides us on the cohorts already created during the previous contract. As noted in our SWOT evaluation and by the committee, the recruitment of a data manager is a major issue: this will be the priority for Team 1 in the next year. We have started to address this issue and identified some solutions. Part of our databases (ongoing project on bipolar disorders) is managed with the help of resources provided by the FondaMental foundation; this collaboration may extend to the data management of future projects. We have also initiated collaborations with Pr S. Chevret (INSERM U717, Paris Diderot University) for the management of the databases that record response to treatment in addiction and bipolar disorders, and with Pr F. Mentré for the population pharmacokinetic data (INSERM U738, Paris Diderot University).

We also agree that the replacement of our administrative manager after her retirement will be also one of the priorities of the Unit and we look forward to our institutions support.

Integration between clinical and non-clinical teams:

The report emphasizes the need for integration between clinical and non-clinical teams. The proposed project already includes a mix of both clinical and non-clinical (*i.e* fundamental or experimental) skills in each team to enhance scientific exchanges between clinicians and researchers.

A positive indication that this strategy is not only advisable in the Unit but also intelligible to the scientific community is our recent success (March 2013) in obtaining research grant from the *PRES Paris Sorbonne Cité* (Project *RespoLi*, 150 keuros for three years). This translational research project dedicated to the lithium response of bipolar disorder patients, associates the three future teams integrating clinical, experimental, and basic research work packages.

Based on this example, we are confident that the configuration of the Unit we propose in this project, favoring cross-team collaborations and fruitful productions from bedside to bench and vice-versa, will help us to establish our Unit as an international reference group connecting blood-brain barrier with therapeutic and toxic responses to psychotropic drugs.

Jean-Louis Laplanche
Project leader, *Variability of the response to psychotropic drugs*

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