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

Department for the evaluation of research units

AERES report on unit:

Centre de Recherche de l'Institut du Cerveau et de la Moëlle

CRICM

Under the supervision of the following institutions and research bodies:

Université Paris 6 – Pierre et Marie Curie

Centre National de la Recherche Scientifique

Institut National de la Santé et de la Recherche Médicale

January 2013

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

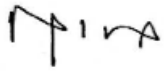
Research Units Department

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.
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 following grades:

- Grading table of the unit: Centre de Recherche de l'Institut du Cerveau et de la Moelle - CRICM

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

- Grading table of the team: ALS causes and mechanisms of motor neuron degeneration

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

- Grading table of the team: Molecular basis, physiopathology and treatment of neurodegenerative diseases

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

- Grading table of the team: Alzheimer's and prion diseases

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

- Grading table of the team: Experimental therapeutics of Parkinson's Disease

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

- Grading table of the team: Control of normal and abnormal movements

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

- Grading table of the team: Cellular physiology of cortical microcircuits

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

- Grading table of the team: Excitability and Dynamics of Neuronal Assemblies

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

- Grading table of the team: Neurogenetics and physiology

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

- Grading table of the team: Genetics and physiopathology of epilepsy

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

- Grading table of the team: Cortex & Epilepsy

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

- Grading table of the team: Optogenetic dissection of signal circuits underlying locomotion

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

- Grading table of the team: Experimental neuro-oncology

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

- Grading table of the team: Mechanisms of myelination and remyelination in the central nervous system

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

- Grading table of the team: Functions and development of microglia

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

- Grading table of the team: Molecular and cellular approaches of myelin repair

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

- Grading table of the team: Development of oligodendrocyte and neurovascular interactions

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

- Grading table of the team: PICNIC: Physiological Investigations of Clinically Normal and Impaired Cognition

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

- Grading table of the team: Cognition, neuroimaging and brain diseases

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

- Grading table of the team: Social and Affective Neuroscience

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

- Grading table of the team: Behavior, emotion, and basal ganglia

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

- Grading table of the team: Motivation, brain and behavior

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

● Grading table of the team: ARAMIS: Algorithms, models and methods for images and signals of the human brain

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

● Grading table of the team: Biotechnology and biotherapy

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

Evaluation report

Unit name:	Centre de Recherche de l'Institut du Cerveau et de la Moelle
Unit acronym:	CRICM
Label requested:	UPMC, INSERM, CNRS
Present no.:	CRICM, UPMC-Paris6, UMR_S 975, Inserm U 975, CNRS UMR 7225
Name of Director (2012-2013):	Mr Bernard ZALC
Name of Project Leader (2014-2018):	Mr Alexis BRICE

Expert committee members

Chair:	Mr Dimitri KULLMANN, UCL, UK
Experts:	Mr Francesco BATTAGLIA, Amsterdam, Holland
	Mr Abdelhamid BENAZZOUZ, Bordeaux, (CoNRS representative)
	Mr Francois BERGER, Grenoble
	Mr Christophe BERNARD, Marseille
	Mr Wolfgang BRUECK, Göttingen, Germany
	Mr Luc BUEE, Lille, (INSERM representative)
	Mr Gaetano FINOCCHIARO, Milano, Italy
	Ms Elizabeth FISHER, UCL, UK
	Mr Masud HUSAIN, Oxford, UK
	Mr Salvador MARTINEZ, Alicante, Spain
	Mr Jan SCHWAB, Berlin, Germany
	Mr Gabor TAMAS, Szeged, Hungary
	Mr Denis VIVIEN, Caen, (CNU representative)

Scientific delegate representing the AERES:

Mr Laurent GROC

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

Ms Claire GIRY (INSERM)

Mr Paul INDELICATO (UPMC)

Mr Bernard POULAIN (CNRS)

1 • Introduction

History and geographical location of the unit:

The Centre de Recherche de l'Institut du Cerveau et de la Moelle (CRICM) was created in January 2009, under the auspices of the UPMC, INSERM (Institut National de la Santé et de la Recherche Médicale) and the CNRS (Centre National de la Recherche Scientifique). It is located on the Pitié-Salpêtrière campus and hosts 21 academic research teams, selected after evaluation by the AERES. The research teams are organized along 4 thematic axes (Neurodegeneration; Excitability, Synapses and Associated Pathologies; Development, Glial Pathology and Repair; and Cognition, Emotion and Behaviour) plus a methodological pole, each coordinated by two leaders.

The axes were defined according to the profiles of the research teams. In 2011, four teams, headed by Mr Albero BACCI, E. KABASHI, Mr Mathias PESSIGLIONE and Ms Claire WYART, joined the Institute after an international call in 2010 and selection by the Scientific Advisory Board. Three obtained ATIP/Avenir Programme grants (Inserm/CNRS) (Mr Mathias PESSIGLIONE, Ms Claire WYART, E. KABASHI) and three ERC starting grants (Ms Claire WYART, Mr Mathias PESSIGLIONE and Mr Alberto BACCI). In 2011, they were joined in the new ICM building by the 18 CRICM teams. Between 2011 and 2012, two new ATIP/Avenir teams (E. HUILLARD and B. LAU) joined the Institute.

Management team:

Mr Bernard ZALC - INSERM, Director, Mr Etienne HIRSCH –CNRS, Vice-director, Mr Laurent COHEN - UPMC-P6/AP-HP, Scientific advisor for clinical research, Mr Philippe ALCOUFFE - UPMC-P6, Administrative and Financial director.

AERES nomenclature:

SVE1_LS5, SVE1_LS4, ST6, SVE1_LS7, SVE1_LS2

Unit workforce:

Unit workforce	**Numbers at 30/06/2012**	**Numbers at 01/01/2014**	2014-2018 **Number of project producers**
N1 : Permanent professors and similar positions	44	43	
N2 : Permanent researchers from Institutions and similar positions	55	52	
N3 : Other permanent staff (without research duties)	135	122	
N4 : Other professors (Emeritus Professor, on-contract Professor, etc.)	5	9	
N5 : Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	73	163	
N6 : Other contractual staff (without research duties)	100	75	
TOTAL N1 to N6	412	464	

Percentage of producers	***100,00 %***

All researchers are producers

Unit workforce	Numbers at 30/06/2012	Numbers at 01/01/2014
Doctoral students	79	
Theses defended	62	
Postdoctoral students having spent at least 12 months in the unit*	24	
Number of Research Supervisor Qualifications (HDR) taken	18	
Qualified research supervisors (with an HDR) or similar positions	74	74

2 • Assessment of the unit

Strengths and opportunities:

The unit benefits from a world-class infrastructure, with state-of-the-art facilities for experimentation on rodents, zebrafish and non-human primates, on-site viral vector production, future proximity to a large biobank, and an important neuroimaging platform (CENIR MRI and MEG-EEG). It benefits also an easy access to one of Europe's largest hospitals specialising in neurological disease.

Its core scientific teams were selected from among existing research groups on the Pitié-Salpêtrière campus. Further teams were created by pump-priming by the ICM foundation, by recruiting a number of young scientists who subsequently obtained ATIP/Avenir funding.

This recent history leads to the expectation that the teams within the unit should be well above average. Their co-location within a very well equipped building, whose running costs are subsidised by the foundation, should foster some exciting new research collaborations.

Weaknesses and threats:

Despite the new opportunities, the scientific teams are, to some extent, continuing to work in relative isolation from one another, even though similar topics are in some cases being pursued by more than one team. The unit is also somewhat remote from some of the world-class science in related disciplines elsewhere in the Paris area.

Much of the recent high-profile work from the unit's teams has centred on genetics. However, classical genetic methods may be insufficient to continue to identify variants with strong effects in neurological disease. The Unit does not have world-class bioinformatics on site. Local expertise in the roles of altered non-coding RNA expression and RNA processing is also patchy and mainly targeted to metabolic disease. Similarly, some of the teams that have previously been very successful in identifying genes appear to be experiencing difficulties in making an impact in studying the molecular and cellular mechanisms downstream from the mutations.

The unusual alliance of public and private funding has contributed to a lack of clarity about lines of reporting and command within the unit. Different contracts of employment for support staff in different teams can lead to friction.

The overall scientific strategy of the Unit does not appear to have been defined with the supervising bodies and supporting institutes. A simple focus on excellence of individual teams has advantages and disadvantages.

The committee heard that the ethical review process can be cumbersome, even for non-clinical studies on human subjects.

Recommendations:

The committee suggests that a single, simplified and transparent governance structure should be put in place, and endorsed the proposal that Mr Alexis BRICE direct the unit.

The committee considers it important that the Unit formulates a medium to long-term strategy to focus recruitment of new teams and management of existing teams that may require reconfiguration to improve synergies of the existing expertise. Several teams would benefit from high-level bioinformatics. Appointment of an expert in this area should be managed in such a way as to allow him or her to collaborate freely with several teams.

If the unit decides to commit to clinical trials it will require the establishment of a clinical trials office and academic appointments in the evaluation of outcomes.

3 • Detailed assessments

Assessment of scientific quality and outputs:

The unit published 1230 papers in peer-reviewed journals since 2009. Among the most important papers that were led by researchers from the Unit (as first and/or corresponding author) since 2008 are: Bekinschtein et al., PNAS 2009, Boillée S, Cleveland DW. JCI 2008, Brochard et al., JCI 2009, Dehaene et al., Science 2010, Depienne et al., PLOS Genet 2009, El Hallani et al., Brain 2010, Gaillard et al., PLOS Biol 2009, Huberfeld et al., Nat Neurosci 2011, Kiebe et al., Brain 2012, Lebreton et al., Neuron 2009, Lobsiger et al., PNAS 2009, Lorenceau et al., Curr Biol 2012, Mallet et al., NEJM 2008, Marinelli et al., Nature Neurosci 2009, Mochel et al., Ann Neurol 2012, Palminteri et al., PNAS 2009; Brain 2011, Pessiglione et al., Neuron 2008, Schmidt et al., Brain 2008; PLOS Biol 2012, Soussain et al., Lancet 2009, Stankoff et al., Ann Neurol 2011, Tepavcevic et al., JCI 2012, Vidailhet et al., Lancet Neurol 2009, Wyart et al., Nature 2009, Zujovic et al., PNAS 2011.

The productivity of individual teams is however not uniformly high. A small number of teams have either published only in specialised journals or principally in collaboration with large research consortia elsewhere, making it difficult to evaluate their scientific contribution. The committee nevertheless considers it a strength of the Unit that several teams are well integrated with international neurogenetics collaborations.

Assessment of the unit's academic reputation and appeal:

Many of the teams that make up the Unit contributed to the international profile of the Pitié-Salpêtrière Hospital, which has been ranked 5th in European Neuroscience by the Times Higher Education for citations by paper.

At present, it is difficult to separate the international recognition of the Unit from that of the Pitié-Salpêtrière Hospital and co-located pre-existing research units. Nevertheless, several of the senior researchers who currently lead these teams or have led them in the past have an outstanding reputation, as witnessed by International Prizes (e.g. Sobeck Prize 2010; Prix Roger de Spoelberch, 2012). Several researchers have also been recognised by the award of French prizes such as the NRJ – Fondation de France.

Members of the Institute participate in editorial boards of scientific or medical journals, including: PLOS Biology, Lancet Neurology, J ClinOncol, Brain, EMBO J, Hum Mol Genet, Arch Neurol.

ICM researchers participate in international scientific advisory boards including: Montreal Neurological Institute, FTN University of Mainz, Oxford Parkinson's Disease Centre, Cambridge Center for Myelin Repair, Edinburgh Center for Translational Research.

They are also on the boards of International learned Societies: e.g. Movement Disorders Society, European Neurological Society, European Society of Human Genetics, Myelin Project.

The ICM Foundation permitted the recruitment of several young researchers who have since obtained ATIP/Avenir awards and are being evaluated in this report. These young researchers have been highly successful and are gaining international recognition, as witnessed by prestigious grants (in particular from the European Research Council).

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

Researchers from the Unit have applied for or received 21 patents and several spin-off companies have been formed. Several collaborations with industry have been established, and the Unit received the CARNOT certification in 2011 to recognise this. Several researchers have high-profile roles in national and international disease-specific bodies (e.g. A. Baron, presidency of the French Glial Club).

Some of the leaders are also actively engaged in patient support groups, including the presidency of ARSEP (French Multiple Sclerosis Association – C. Lubetzki).

Assessment of the unit's organisation and life:

The unit is organised along 4 Scientific Axes (Neurodegeneration; Excitability, Synapses and their Disorders; Development, Glial Pathology and Repair; and Cognition, Emotion and Behaviour), with a 'Transversal' Axis consisting of three research teams.

These are focused on methods development (ARAMIS – which deals primarily with computational image analysis and integration of multimodal datasets; Biotechnology and Biotherapy – which deals with molecular tools for manipulation of gene expression; and an Optogenetics, Physiology and Behaviour team).

Rapid progress has been made in facilitating interactions among students and postdoctoral researchers in different teams, and the Committee understood that there is an abundance of opportunities for social and scientific contacts at the junior level spanning the entire Unit.

The complex relationship between the ICM foundation, CNRS, INSERM and University has generally been managed successfully, although the governance structure is not fully transparent to some junior researchers and technical and engineering staff. The Committee also heard that there was insufficient clarity regarding such matters as criteria for promotion and bonuses for technicians and engineers.

The committee heard that relatively few students are going to international and national meetings, with haphazard access to support for travel and registration. Postdocs and PhD students also mentioned some lack of clarity regarding authorship of papers.

The individual scientific teams vary considerably in size and are still scientifically relatively isolated from one another, resulting in some anomalies, such as a small research group consisting of one or two people within one team working on a problem in relative isolation from another group of researchers in another team.

The unit's strategy is relatively unfocused at present. It cannot cover comprehensively the entire area of basic and translational neuroscience. The priority at present appears to be the recruitment and consolidation of researchers who publish successfully. This may be a sensible 'hands off' approach to allow the Unit to attain a high level of international visibility, but it does not necessarily take advantage of the unusual location and intimate relationship with the Pitié-Salpêtrière hospital to maximise the potential translation of discoveries for patient benefit.

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

There are many PhD and Masters students, and many of the most productive researchers have a heavy teaching load. Some of these researchers balance research and teaching with clinical responsibilities. The MD/PhD program is one of the teaching highlights of the institution and is coordinated by one of the PIs.

Overall, the Committee was impressed by the amount of teaching at all levels (both non-clinical and clinical) being carried out by researchers.

Assessment of the five-year plan and strategy:

The unit's short-term strategy is to consolidate its scientific strengths, with a planned recruitment drive led by the ICM Foundation. The specific areas to be targeted were not evident, but the additional funding provided by the IHU may allow leverage of resources. At this stage, the priority appears to be focused on scientific excellence as evaluated by publications in high-profile journals.

The long-term strategy is less clear. There are opportunities to apply scientific discoveries for patient benefit, but this would require a more concerted effort to focus on a small number of disease areas. There is a Clinical Investigation Unit on site, which could facilitate clinical trials. However, a concerted effort to undertake clinical trials would require substantial investment both in administrative support (a clinical trials office) and possibly the appointment of academics working on outcome measures.

4 • Team-by-team analysis

Team 1 : ALS causes and mechanisms of motor neuron degeneration

Name of team leader: Ms Séverine BOILLEE

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		2	
N2: Permanent EPST or EPIC researchers and similar positions		4	
N3: Other permanent staff (without research duties)		1	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		8	
N6: Other contractual staff (without research duties)		1	
TOTAL N1 to N6		**16**	

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:

This is a new team proposed for 2014-2018. The papers published by the researchers were therefore principally as part of previous affiliations. In particular, the group leader high-profile papers (including PNAS) were published as a post-doctoral researcher. The earlier Science paper has been cited over 600 times. The output spans both clinical and basic research, with clinical cases through to genetics through to molecular biology, and this is a powerful combination to make an impact in ALS mechanisms. There is one paper in Neural Transmission (2010) where the group leader is the senior author. Another group member is the first and corresponding author in a paper in J Med Genet (2012), and previously published first-author papers in PNAS and J Med Genet.

Assessment of the team's academic reputation and appeal:

The team leader is increasingly recognised and several of the permanent staff have obtained external funding from national organisations. The group leader and an investigator have been awarded an "NRJ-Institut de France" prize. The team has also established several international collaborations.

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

Good clinical ties to other ALS centres in France, UK and Canada for identification of new causal genes through collections in other clinical centres. This would be a good basis for clinical trials and for testing of novel targets with relevance for industry/biotech.

Assessment of the team's organisation and life:

This is a new team so the team organisation is difficult to assess.

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

The combination of basic science and neurodegeneration provides a valuable environment for training researchers in an area of major economic and social impact. Several PhD and Master students were trained by the staff of the team. Members of the team are co-responsible for the education work package of the Translational Neuroscience Institute of Paris (IHU), Coordination of mobility for the student at the UPMC University of Medicine, Vice President of the International Relations at UPMC.

Assessment of the five-year plan and strategy:

The team is focussed on a few key questions and either has the in house expertise to address these questions or is forming strategic collaborations externally. There is an exciting and potentially very productive time ahead when the group is physically located in the same place as of January 2014.

In the last five years the ALS research field has changed dramatically as three major genes plus several potentially minor affect causative genes have been found, implicating RNA metabolism, and the field changed again in 2011 with the discovery of the expanded hexanucleotide repeat in the C9orf72 gene. It is now impossible to cover all angles in ALS research and the team is focussing on the role of peripheral macrophages, investigating C9orf72, including through animal models, and using its clinical strengths to identify other ALS genes in familial forms of the disease. It is entirely sensible to focus in this way and the team has picked important questions to look at, in particular assessing the role of macrophages and whether these may provide routes to therapy. The development of an iPS cell bank could also be particularly powerful, although it is not clear how large this bank would be and what its availability would be to external users. The group is well integrated into the European ALS networks to capitalise on other mouse models.

Some of the proposed experiments have already been partially published by other teams (Liu et al., 2012, Am J Neurodegen; and in Fiata et al. 2010 with a microarray exploring 28.869 genes). This is a competitive area.

Conclusion:

- Strengths and opportunities:

This is a young enthusiastic team that has a good complementarity of methods. There is expertise in microglial biology elsewhere in the ICM. The overarching aim of the projects is to dissect the toxic and protective components of pathological neuro-glia interactions in ALS with the ultimate goal to define novel molecular pathways for intervention. This is a powerful and original combination.

Two of the PIs have an international reputation, and they have forged internal and international collaborations.

- Weaknesses and threats:

This is a competitive area of research and other models of C9orf72 ALS are being developed.

Some other teams are working on overlapping topics.

- Recommendations:

The team should be encouraged to build on their strengths.

4 • Team-by-team analysis

Team 2 : Molecular basis, physiopathology and treatment of neurodegenerative diseases

Name of team leader: Mr Alexis BRICE

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	4	4	
N3: Other permanent staff (without research duties)	5	4	
N4: Other professors (PREM, ECC, etc.)		2	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	5	14	
N6: Other contractual staff (without research duties)	16	16	
TOTAL N1 to N6	35	45	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	8	
Theses defended	4	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	4	
Qualified research supervisors (with an HDR) or similar positions	8	7

• Detailed assessments

Assessment of scientific quality and outputs:

This is a large team with an outstanding reputation, which has previously identified several genes responsible for neurodegenerative diseases. They continue to publish at a high rate (253 original articles including Lancet and Nat Genetics) in particular in spinocerebellar ataxia and Parkinson's disease genetics, although many of the high-profile papers have arisen from international collaborations, diluting the precise scientific contribution of the team. Those papers where the team has been the clear or main scientific driving force include some in Brain and Annals of Neurology.

Assessment of the team's academic reputation and appeal:

The group leader and its colleagues have a world-class reputation in SCA and Parkinson's disease genetics. They have been invited for lectures in international conferences, and have established collaborations across Europe and further afield. The team has secured over 14 million Euros of funding from national and international institutions and charities.

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

The team successfully collaborates with a pharmaceutical laboratory.

Assessment of the team's organisation and life:

Team members have successfully managed teaching, management and clinical service commitments. In addition, the leader of the team has also successfully led the complex reconfiguration of the CRICM and alignment with ICM and IHU.

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

There is a highly successful track record of supervision of PhD and Masters students, many of whom have gone on to obtain permanent positions. The group leader is co-coordinator of the M2 module "Medical Genetics" at UPMC, and other team members participate in the Master in Integrative Biology and Physiology.

Assessment of the five-year plan and strategy:

The team proposes to work on three main disease areas:

- Spinocerebellar degeneration (with a focus on genetics and cell biology, pursuing consequences of spatacsin/spastizin mutations; SCA7-ataxin7 antisense; biomarkers and NMR spectroscopy; and SPG5 cholesterol metabolism),
- Parkinson's disease (genetics, biomarkers, mitochondria),
- FTLD (genetics, biomarkers, models including a C9orf72 mouse).

The first two are strong, with clear hypotheses and plans of investigation. The third is based on less advanced pilot data. Although it is related to the work of team 1, explicit links are not evident.

Conclusion:

- Strengths and opportunities:

The team have access to large patient cohorts and set a track record of international collaborations. The interaction with the hospital is excellent. The team as a whole has a critical mass with world-class reputation.

This combination of clinical resources, track record and external funding puts the team in an excellent position to continue to make breakthroughs in the discovery of new genes underlying neurodegenerative disorders and to understand disease mechanisms.

- Weaknesses and threats:

The team is building strengths in cell biology and bioinformatics but these aspects could still be improved. The PIs have identified signalling pathways that may provide targets for novel therapies, and one of these has led to a clinical trial (cholesterol metabolism in patients with SPG5 mutations), but the translational pathway has a high attrition rate, and the team's current standing in disease mechanisms has yet to match its reputation in gene discovery.

- Recommendations:

This team, in common with others in the unit, would benefit from expertise in bioinformatics to help analyse polygenic variability in neurodegenerative diseases. The team should be encouraged to continue to invest in biochemical and cell biological methods to investigate pathways downstream of the mutated genes, in order to maximise the prospects for therapeutic interventions.

4 • Team-by-team analysis

Team 3 : Alzheimer's and prion diseases

Name of team leader: Mr Stéphane HAIK et Ms Marie-Claude POTIER

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	3	3	
N2: Permanent EPST or EPIC researchers and similar positions	3	3	
N3: Other permanent staff (without research duties)	4	5	
N4: Other professors (PREM, ECC, etc.)		1	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	6	13	
N6: Other contractual staff (without research duties)	1	2	
TOTAL N1 to N6	17	27	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	4	
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	2	3

• Detailed assessments

Assessment of scientific quality and outputs:

The team has 150 publications in the reporting period (41 directly attributable to scientific leadership by the team). They have published 16 Editorials. The papers led by the team have appeared in journals such as Acta Neuropathol, Annals of Neurology, Hum Mol Genet, Neurobiol Aging. Other papers published in collaboration have appeared in journals including JCI and Lancet Neurol. This is a substantial output when taking into account the number of people (3 full-time researchers, 3 researchers with teaching and/or clinical duties and 2 clinicians).

Assessment of the team's academic reputation and appeal:

Members of the team receive many invitations to international meetings. The team is integrated in several international collaborations, mainly related to neuropathological diagnostic criteria, and participates in several projects funded by the ANR, EU-FP7, and other national and European bodies.

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

Three patents are held by the team, and they have received grants from LFB and Roche.

Assessment of the team's organisation and life:

Nothing specific to mention, except that Haik and Potier appear to function relatively independently.

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

Highly successful track record of teaching and training in a economically and socially important area.

Assessment of the five-year plan and strategy:

The core project that has the highest potential for important breakthroughs centres on the interactions between cholesterol metabolism, PrP and Abeta cascades. The team has established collaborations and methodologies that are appropriate to pursuing this area, where the PIs have an established reputation. The Committee considered this deserving of greater concentration of resources. Abeta imaging in vivo is an area where the team may have more difficulty establishing an international reputation because of competition. The projects surrounding prions are relatively speculative and high-risk.

Conclusion:

- Strengths and opportunities:

The team is focused on understanding neurodegenerative pathways and has strong links to the clinic. There is a steady output of solid publications. The succession to the previous PI (C Duykaerts) has been managed successfully, and the team has an international reputation in the study of mechanistic links between cholesterol and Abeta.

- Weaknesses and threats:

The different groups within the team appear to be working relatively independently, and the publication output could be improved. Animal models are not used to their full potential. The projects on prions are high-risk and in vivo imaging of Abeta is a competitive area.

- Recommendations:

The committee considered the work on cholesterol and Abeta the strongest. The expertise in molecular and cellular biology could be improved. A greater emphasis on animal models should be considered.

4 • Team-by-team analysis

Team 4 : Experimental therapeutics of Parkinson's Disease

Name of team leader: Mr Etienne HIRSCH

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	2	2	
N2: Permanent EPST or EPIC researchers and similar positions	5	4	
N3: Other permanent staff (without research duties)	6	6	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	4	6	
N6: Other contractual staff (without research duties)	5	5	
TOTAL N1 to N6	22	23	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	6	
Theses defended	5	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	7	5

• Detailed assessments

Assessment of scientific quality and outputs:

The number and quality of the publications from this group are high, with many successful publications coming from collaborative projects. The projects where the team is clearly leading have resulted in publications in J Clin Invest (x2), Brain and PNAS, as well as in more specialised journals such as J Neurochem, J Neurophysiol, Arch Neurol, and Mov Disord.

Assessment of the team's academic reputation and appeal:

M. Etienne HIRSCH is among the most frequently cited researchers in the field of Parkinson's disease worldwide, especially for the role of inflammation in disease progression.

The team is extensively involved in external scientific and extra-scientific activities as evidenced by numerous collaborations, editorial activities and the organization of meetings. This activity has received recognition in the form of several prizes and nominations to coordinate activities.

The team has secured external grants at national (ANR) and European (FP7) levels. There are collaborations with both national and international partners.

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

The team has extensive links with Industry, both pharmaceutical and in other fields. Eight patents have been filed, including 2 which were commercialised. The team is involved in clinical trials. They have external grants from national and international (EU FP7) bodies, and from charities. The income from external sources since 2007 is excellent. Patented results and intense industrial partnerships.

Assessment of the team's organisation and life:

The team is run successfully and has contributed to the unit's reorganisation. M. Etienne HIRSCH is vice-Director of the CRICM.

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

During the reporting period the team has trained a substantial number of students (13 Masters; 5 completed PhD). Six PhD students are currently enrolled. Unusually one PhD student obtained a grant from the "Collège des ingénieurs" to pursue an MBA in parallel. Another received competitive award (Bourses L'Oréal France – UNESCO "Pour les Femmes et la Science"). Previous PhD students have moved on to positions elsewhere (neuropsychologist at Charles Foix hospital, chief resident leading to a permanent PH position, and two in postdoctoral positions abroad).

The team members are also strongly involved in the organization of Masters courses.

Assessment of the five-year plan and strategy:

There is a coherent strategy that is likely to yield important advances. The clear focus of the work programme documents attests to the scientific coherence of this team. The committee welcomed the proposal to undertake clinical trials, although trial methodology is not a strength of the CRICM.

Conclusion:

- Strengths and opportunities:

The team and group leader have strong international recognition in the field of Parkinson's disease and movement disorders. Researchers with clinical and/or basic science background are working together with a multidisciplinary approach ranging from cellular biology to neurochemistry, electrophysiology, functional neuroanatomy, and animal behaviour. There is evidence of continuity from bench to bedside, with a clear path from cell cultures, through animal models and to human subjects. The team has published articles with high citations.

- Weaknesses and threats:

There are relatively few postdoctoral positions in the team.

- Recommendations:

The team should consider investing further in cellular and molecular pathways. The team may also benefit from formal links with experts in clinical trial methodology.

4 • Team-by-team analysis

Team 5 : Control of normal and abnormal movements

Name of team leader: Ms. Marie VIDAILHET & Mr Stéphane LEHÉRICY

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	4	4	
N2: Permanent EPST or EPIC researchers and similar positions	3	3	
N3: Other permanent staff (without research duties)	5	3	
N4: Other professors (PREM, ECC, etc.)	1		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	7	
N6: Other contractual staff (without research duties)	2	3	
TOTAL N1 to N6	17	20	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	5	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	7	6

• Detailed assessments

Assessment of scientific quality and outputs:

In the past five years (2007-2012), the team focused on the characterization of the cortical and subcortical networks involved in normal and pathological motor control and on the identification of potential targets for therapeutic strategies of movement disorders. They have used a translational approach (from animal exploration towards human disorders) with a synergy of basic scientists and clinicians devoted both to research and care. The models used were primates, healthy volunteers and patients suffering from motor disorder diseases.

The team is innovative with clinical relevance towards public health. They demonstrated the beneficial effect of Deep Brain Stimulation in dystonia, contributed to technological advances for the exploration of cerebello-cortical connectivity and developed non-invasive modulation of these pathways with improvement of tremor.

During the last five years the team published 195 articles, in 25 of which team members had last or first authorship, including Lancet Neurol, Am J Hum Genet, Arch Gen Psychiatry, Ann Neurol, Brain, Neurology, J Neurosci, Sleep Med, and Cereb Cortex. In addition, they have published a large number of papers in collaboration with other local, national and international teams.

Assessment of the team's academic reputation and appeal:

The team has an excellent national and international visibility.

Senior members of the team have participated as Invited Speakers in international conferences (AAN, ENS, EFNS, MDS, International Dystonia Symposium, 2011, World Association of Sleep Medicine; International workshop on synaptic plasticity – 2010; Advanced Body Imaging Course at the ISMRM 18th Annual Meeting 2010, etc.) and were responsible for the Organisation of large international conferences (Movement disorders Society, Paris, 2009).

Members of the team are on the boards of several international learned societies (Movement disorders Society, European Neurological Society), and hold a substantial number of grants including from French (ANR, FRM, ANR-emergence, Carnot, DGOS Inserm, FRC, France Parkinson) and international bodies (Dystonia Coalition).

The team leader is also on the steering committee of the Dystonia Coalition-NIH partnership.

The team also has international collaborations including with Caltech, NIH Human Motor control section, Bethesda, Washington, Center for Magnetic Resonance Research, University of Minnesota, USA.

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

The team has important interactions with the public, including representation on the Scientific committee of France Parkinson, AMADYS, Alliance France Dystonie (Dystonia), APTES (essential tremor), AFGTS (Gilles de la Tourette), and GROUPAMA (colloquium on rare diseases)

Different members of the team are actively involved in national health care specific programs (appointed mission from the Health minister to build up a National Plan in Parkinson's Disease).

Assessment of the team's organisation and life:

The proposed team is composed of 4 permanent MD Professors (PU-PH), 2 MD (PH), 2 permanent EPST Researchers (1 DR2 and 1 CR1), 3 permanent EPST Research Engineers, 1 permanent Assistant Engineer, 2 Post-Docs, 3 MD PhD students, 3 PhD students and 6 Master students. They are already present and working in the team with long-standing collaboration. They are organized in four main research sub-groups providing complementary research expertise and technological approaches. The presence of such permanent academic staff with post-doc fellows and PhD students is an excellent indicator of the dynamism of the team.

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

The team is involved in research training :

- PhD students: 4 are on-going, 5 completed concretized their work with several peer-reviewed publications as 1st author and obtained grants for their research.

- Masters students: 16 were trained in the team

- Several senior members of the team contribute to neuroscience degree courses in the university (Master degree, PhD program, UPMC University).

Assessment of the five-year plan and strategy:

The project is a logical continuation of the team's work, and is ambitious, with clear clinical relevance and a well-reasoned experimental strategy.

The main objective is to investigate normal and pathological motor control from the identification of networks underlying normal and abnormal motor control towards restoration of near-to-normal activity through modulation of the identified networks. The studies will be carried out in non-human primates, healthy subjects and patients with Parkinson's disease, dystonia and Tourette syndrome to identify structural and functional markers. Finally, the team plan to develop new therapeutic approaches. The tools that will be used are non-invasive brain stimulation techniques, EMG, imaging techniques including structural and functional MRI, spectroscopy and magneto-encephalography.

The project is a logical continuation of the team's work. It is very ambitious with high impact and clear clinical relevance. The experimental strategy is well reasoned.

Conclusion:

- Strengths and opportunities:

Excellent and experienced team with synergistic interaction between the different members of the team. The two team leaders as well as the other senior members have an excellent level of publications with a high level of national and international visibility. All necessary equipment to achieve the proposed project is in place. Strong potential in neurophysiology with complementary expertise from experimental primate to human imaging and neurophysiology. Large recruitment of patients in movement disorders by experienced clinicians involved in National Reference Centres and National networks (multicentre studies).

- Weaknesses and threats:

The links between non-human primate models and human studies have not been pursued to their full potential. There appear to be difficulties filling non-permanent positions for young researchers especially in the field of physiology and neuroimaging. The team is very active in training PhD students and postdocs. Long-term external grant income could be secured for the future.

- Recommendations:

The team should consider enhancing the links between non-human primate models and human studies. They are in a unique position in having a close integration of human and non-human primate work, with a close link to the clinic, and should be encouraged to capitalise on this to obtain more substantial external grants.

4 • Team-by-team analysis

Team 6 : Cellular physiology of cortical microcircuits

Name of team leader: Mr Alberto BACCI

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			
N2: Permanent EPST or EPIC researchers and similar positions	1	1	
N3: Other permanent staff (without research duties)			
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	5	5	
N6: Other contractual staff (without research duties)	1	1	
TOTAL N1 to N6	7	7	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	0	
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	1	1

• Detailed assessments

Assessment of scientific quality and outputs:

The team leader set up a successful laboratory in Rome before moving to ICM where he published in high profile journals, including Nature Neuroscience and PLOS Biol. He has managed the move from Rome without loss of productivity.

Assessment of the team's academic reputation and appeal:

The team leader has attracted funding from extremely competitive grant schemes (ERC) and has an excellent international reputation. He is on the editorial board of PLOS Biology.

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

N/A

Assessment of the team's organisation and life:

This is a relatively young and small team. Nothing specific to mention regarding this criteria, everything seem to proceed smoothly.

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

Previous PhD students and postdocs from the laboratory in Rome have successfully found positions in several countries.

Assessment of the five-year plan and strategy:

There is a mixture of high-risk and safe projects. The PI proposes a plan that appears as a logical continuation of his previous efforts in an increasingly competitive field. Some of the projects are imaginative and depend on methodological developments, which are likely to lead to interesting results. There is competition in the fields of endocannabinoid- and nitric oxide-mediated plasticity. There is a developmental project that aims to understand the interaction between GABA receptor subunits and the innervation of different compartments of principal cells by distinct types of interneurons. This is acknowledged by the author to be high-risk but the team has established in utero electroporation and has access to appropriate tools. The team has also linked up with experts in in vivo recordings.

Conclusion:

- Strengths and opportunities:

The group leader has an excellent track record and to a large extent, well established methodology. A young, dynamic team with a group leader of proven qualities and flexibility. The publication list is excellent (Nat Neurosci, J Neurosci, PLoS Biol). Well designed research programme, logical follow-up of past projects.

- Weaknesses and threats:

Making the next step up to in vivo work will require substantial additional investment. There are nevertheless well developed plans for applying for such funding and excellent collaborators. Intense competition in some areas of the proposal, but this is to be expected at this level. The developmental project is high-risk, and the mechanistic hypothesis is vague. GABA has a trophic action and this may act as a confounding factor.

- Recommendations:

The proposal to move into in vivo work is sensible, but the team should try to identify a behavioural parameter that can be measured or manipulated to relate to the cellular phenomena that they study.

4 • Team-by-team analysis

Team 7 : Excitability and Dynamics of Neuronal Assemblies

Name of team leader: Mr Stéphane CHARPIER

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	1	3	
N2: Permanent EPST or EPIC researchers and similar positions	2	2	
N3: Other permanent staff (without research duties)		1	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		3	
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	3	9	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	3	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	0	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	2	2

• Detailed assessments

Assessment of scientific quality and outputs:

This group moved to the ICM in Sept 2011. It focuses on absence seizures with in vivo physiology (with a focus on intrinsic plasticity), and on the analysis of human focal epilepsy (with a strong mathematical component).

The group has published in respectable journals (J Neurosci, J Physiol, Brain). The number of publications with first or last authorship is not high, but studying spontaneous seizures in rodents is difficult and this group is among very few in the world to do this successfully. Furthermore, the publication record should take into account the heavy teaching load of the team leader (169 h).

A clinical epileptologist published as a first author in Nature Neuroscience when he was in another laboratory. A senior team member has published some highly original papers on sophisticated analysis of EEG including a paper in Brain.

Very few groups in the world have access to human tissue for electrophysiology.

Assessment of the team's academic reputation and appeal:

The team has yet to secure major international funding, and external French grant support could be stronger. The team's international visibility could be improved. A senior member of the team has a recognized international stature for information processing and mathematical analysis of EEG and single unit activity. He coordinated a European project on seizure prediction.

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

N/A

Assessment of the team's organisation and life:

Nothing specific to mention.

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

The team leader has a very heavy teaching load and coordinates 3 Bachelors and 4 Masters programmes in the University.

Assessment of the five-year plan and strategy:

The ability to perform detailed electrophysiological recordings with quantitative modelling and analysis is powerful. However, this could be complemented by modern methods to target individual cell types and manipulate their excitability. The two main strands (absence seizures in rodents and focal seizures in humans) are relatively disconnected from one another.

The proposal is feasible but its impact may be constrained by the relatively conventional methods proposed, and the correlational nature of the data that will be collected. Other laboratories are beginning to use patch-clamp recordings in awake, behaving but head-fixed animals. More ambitious methods such as this, and optogenetic manipulations, could be considered to raise the ultimate impact of the research. The team could put more attention into identification of the cell types that they propose to record from. There is expertise in many of these methods in teams 6 and 10. Ultimately the interaction of multiple GABAergic components will need to be taken into account in providing a full account of the initiation of seizures. The same comment applies to the study of intrinsic plasticity in vivo. There is competition in the field, with experiments performed in non-anesthetised animals.

The project on human tissue is hypothesis-driven, in continuity with previous research plans. The proposal to use new tools to measure K+ transients is not supported by preliminary data. There is a project to perform advanced analysis of high-frequency oscillations in human focal epilepsy but there is international competition in this field.

The source and quality of the data are not clear. One senior team member is split between this team and team 10, although there is some overlap between projects.

Conclusion:

- Strengths and opportunities:

This is one of the few centres offering a combination of human and rodent epilepsy work, with strong mathematical analysis. There is a demonstrated track record in both fields, and access to human tissue through surgery in the hospital. Very few laboratories are able to study spontaneous absence seizures. There is an interesting and ambitious project that aims for seizure prediction.

- Weaknesses and threats:

The research design is mainly correlational, and does not take advantage of the ability to manipulate neurons at high temporal and spatial precision. The mechanistic underpinning of the phenomena at a molecular level is not being addressed despite the availability of powerful tools within the Unit. The research projects of the team leader and that of two other senior members of the team are relatively independent.

- Recommendations:

The team could put more emphasis on testing the causal relationships between phenomena by perturbing the system. The team should consider complementing in vivo sharp electrode recordings with patch clamp. Recordings in awake, behaving but head-restrained animals could greatly enhance the impact of the work. The combination of clinicians, in vivo electrophysiologists and theoretical scientists is very original. It could be very productive if better integrated.

4 • Team-by-team analysis

Team 8 : Neurogenetics and physiology

Name of team leader: Mr Bertrand FONTAINE & Ms Sophie NICOLE

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	4	3	
N2: Permanent EPST or EPIC researchers and similar positions	3	3	
N3: Other permanent staff (without research duties)	7	7	
N4: Other professors (PREM, ECC, etc.)	1	0	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	1	
N6: Other contractual staff (without research duties)	1	2	
TOTAL N1 to N6	18	16	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	1	
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit	0	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	7	5

• Detailed assessments

Assessment of scientific quality and outputs:

The team has previously identified 7 out of 21 genes responsible for disorders of muscle excitability, and is well integrated in international collaborations, both in muscle channelopathies and in MS genetics. Team members have published a very large number of papers in recent years, although many of these are as part of national or international collaborations, with some dilution of their apparent contribution. Some of these papers have appeared in top-class journals Nature, Cell, Nature Genet, PLOS Genet, Ann Neurol, Brain and J Med Genet. These papers have reported on the genetics of several neuromuscular channelopathies, MS and alternating hemiplegia. It is clearly important to engage in international genetic collaborations and the Committee recognises that this can come at the expense of first/last authorship.The papers where the team clearly took the scientific lead have appeared in Am J Hum Genet, Am J Pathol, Human Mol Genet, and more specialised journals. Among the notable discoveries in this class of publications was the role of agrin mutations in congenital myasthenic syndromes.

The team includes a small group that focuses on the role of P2X7 receptors in Alzheimers and the key paper appeared in JBC. The leader of this group has excellent previous expertise in neuroimmunology.

Assessment of the team's academic reputation and appeal:

One team leader is extremely well connected with MS genetics consortia worldwide where he is involved in all GWAS studies in MS. Both team leaders have extensive collaborations in the field of channelopathies. One provides a clear work program focusing on the genetic causes of muscle channelopathies and the role of sodium channels at the neuromuscular junction. The other heads the Alzheimer project have a less well-developed international profile, and this part of the team's work is being carried out in relative isolation.

The team has an excellent integration with clinicians and collaborators within France, and coordinates three national networks. One team leader is the lead coordinator of the IHU program.

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

The group is a member of, or runs, several networks that interact with clinicians and disease-specific groups across France.

Assessment of the team's organisation and life:

The team appear to work smoothly and they interact with many clinicians both on site and elsewhere.

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

The team has successfully trained masters and PhD students over the last years.

Assessment of the five-year plan and strategy:

There is a quite striking heterogeneity of projects within the team (neuromuscular channelopathies, multiple sclerosis and Alzheimer disease). The introduction of mouse modelling, in collaboration with an expert, seems a sensible approach to support the genetics and in vivo (mouse) analyses are already under way for the neuromuscular excitability programme. The MS programme also is a heavy user of genetics analysis in combination with mouse and cell modelling, although the latter is not as compelling as the genetics approach. Electrophysiology is being strengthened but structural biology may also be relevant to understand the interaction of some of the proteins implicated in neuromuscular diseases.

Some aspects of the lymphocyte biology underpinning the MS project could be stronger. This especially concerns the more functional/mechanistic studies proposed on the role of lymphocyte subpopulations in remyelination. The work programme is based on some as yet unconfirmed speculations on human MS pathophysiology that could be approached by collaboration with other CRICM teams dealing with similar topics. The patient stratification for defining genetically subtypes or therapy responders could be improved and be more detailed, especially regarding therapy response and subtype of MS.

The Alzheimer study is a more focussed analysis of the P2X7R receptor, largely based on mouse models, but is being pursued by a small group of researchers without obvious integration with related research elsewhere in the Unit. The work is at a relatively preliminary stage.

Conclusion:

- Strengths and opportunities:

The neuromuscular project is highly competitive, and the team has excellent links with international consortia both in this area and in MS. The large MS patient cohort followed up by the group with detailed genetic subtyping is an excellent opportunity to identify effects of gene variants on therapy response and other questions. The PI of the Alzheimer project has excellent previous expertise in neuroimmunology, which the entire team and also other groups might profit from.

- Weaknesses and threats:

The disparate research themes do not obviously overlap: neuromuscular excitability, genetic polymorphisms in MS, and P2X7R receptors in Alzheimer disease. The first two are the most developed projects. Genetics of MS: the PI is extremely well connected worldwide. The programme focuses on three topics: interaction of genes with pathways (adhesion molecules, T helper cells), regions undiscovered by GWAS and rare variants. Part 1 requires exact definition of patient characteristics and this does not currently take into account treatment response, especially relevant to the adhesion molecule study. The patient numbers may not be high enough to give definitive results. Concerning the role of T cells in remyelination, this is an interesting hypothesis. However, the assumption that the peripheral lymphocyte profile mirrors the lymphocyte profile in MS lesions is untested. The P2X7R in AD project is relatively limited in its scope, and there is a risk that it will only provide animal evidence supporting a role of inflammation in AD with relatively limited potential for follow-on studies.

- Recommendations:

The channelopathy work is highly promising, and it is sensible to invest in functional expression with patch clamp electrophysiology. The team should consider collaborating with a bioinformatician but this may still require integration with other teams around the world. The MS project may benefit from more detailed characterisation of patients, for instance stratified according to response to therapeutic monoclonals affecting cell migration such as Natalizumab. The more functional/mechanistic studies are at a preliminary stage. The AD project is relatively disconnected, and it may be sensible for this to be done with closer integration with other teams in the CRICM.

4 • Team-by-team analysis

Team 9 : Genetics and physiopathology of epilepsy

Name of team leader: Mr Eric LE GUERN & MS Stéphanie BAULAC

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	1	2	
N2: Permanent EPST or EPIC researchers and similar positions	2	1	
N3: Other permanent staff (without research duties)	5	3	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	3	
N6: Other contractual staff (without research duties)	1	1	
TOTAL N1 to N6	10	10	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	1	
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit	0	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	3	3

• Detailed assessments

Assessment of scientific quality and output:

The publication record in the last 5 years has been successful, with some important contributions in candidate gene and whole exome sequencing in epileptic encephalopathies and related disorders. The work on LGI1 rodents so far has been descriptive but this is a promising platform for a mechanistic analysis and anti-epileptogenic interventions. Team members have published in PLOS Genet, Brain, Hum Mol Genet, J Med Genet, and PNAS (although this paper was on ALS).

The team has recently identified a gene that harbours frequent private mutations associated with focal epilepsy. This has yet to be published but is a very important finding.

Assessment of the team's academic reputation and appeal:

The team has a very good international reputation, having identified two of the first genes in monogenic epilepsy, and team members have participated in the EPICURE programme and are participating in the Euroepinomics consortium. Families with dominantly inherited monogenic epilepsy are however rare, and the team's interests have to some extent broadened to consanguineous families and the role of LGI1 investigated through rodent models. They are accessing consanguineous families with epilepsy from North Africa, and they have a collaboration with a team at Cochin.

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

The team has good links to industry including for translation of diagnostic products.

Assessment of the team's organisation and life:

Although the team is relatively small, there is a mix of clinicians and basic scientists with a good distribution of researchers with different, useful, skills from mouse electrophysiology through to clinical genetics, and collaborations to support this work. The team has established a collaboration with another team of the center that could yield a much more detailed understanding of seizures in the LGI1 KO mouse.

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

They are successfully training Masters and PhD students. The team leader has a busy teaching load in UPMC and runs an Erasmus programme.

Assessment of the five-year plan and strategy:

Monogenic causes of epilepsy are rare but they provide an unrivalled insight into disease processes. It is entirely sensible to capitalise on the wealth of mouse models that are available to understand pathology. The team has established a number of potentially powerful collaborations to perform more advanced analyses of the functional consequences of mutations in several genes including FIG4 and LGI1, but this has yet to lead to high-profile publications. The experiments on conditional deletion of LGI1 are interesting but interpretation of the results may not be clear-cut because the protein is secreted. The team is right to continue to look for rare disease mutations, especially as genome sequencing gets cheaper and easier. The search for genetic modifiers is important, but it is not clear that the team has access to the statistics resource required for this.

The unpublished epilepsy gene is highly interesting and could potentially lead to many important advances.

Conclusion:

- Strengths and opportunities:

The team has an excellent track record, and complementarity of methods. The LGI1 KO mouse is potentially a powerful platform for screening drugs for antiepileptogenic potential. The team has recently discovered a potentially very important epilepsy gene.

● Weaknesses and threats:

No expert in bioinformatics on site. The cell biology could be stronger although there is some expertise. There is intense competition in epilepsy genetics. The work on the LGI1 knock-out mouse and rat has yet to provide a major mechanistic breakthrough. The team is rather small in relation to the proposed research programme.

● Recommendations:

The team is right to invest in biological validation, but may wish to consider the potential of differentiated IPS cells as a window on disease mechanisms. The team should be encouraged to take advantage of the available conditional mouse knockouts the International Mouse Knockout program. They may consider engaging with the pharmaceutical industry to use the LGI1 KO mouse to test potential antiepileptogenic drugs, because there is no good model of human cryptogenic focal epilepsy.

4 • Team-by-team analysis

Team 10 : Cortex & Epilepsy

Name of team leader: Mr Richard MILES & Ms Desdemona FRICKER

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	4	3	
N2: Permanent EPST or EPIC researchers and similar positions	3	3	
N3: Other permanent staff (without research duties)	3	3	
N4: Other professors (PREM, ECC, etc.)	1	1	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	7	
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	13	17	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	1	
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	4	6

• Detailed assessments

Assessment of scientific quality and outputs:

This team has an excellent international reputation although its scientific output has been uneven, as acknowledged in the SWOT analysis. Team members published a very interesting paper in Nat Neurosci that attracted considerable interest in the epilepsy community. Two members are moving to team 7 in the same institute. One of them, who has published some strong papers (Brain), appears to be working with both teams.

Assessment of the team's academic reputation and appeal:

The team leader recently obtained an ERC grant, and was awarded the Basic Science Investigator Award by the American Epilepsy Society. He is regularly invited to international meetings and was on the Wellcome Trust's Neuroscience panel. The team is known for careful work on biophysics, relating the firing of individual neurons to the generation of field potentials, and the integration of ex vivo and intracranial recordings is an extremely important contribution. The work on presubiculum has yet to gain widespread recognition although one of the team leaders has identified some interesting mechanisms.

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

This is a specialised field that does not lend itself easily to public engagement, but the work is highly relevant to the diagnosis and management of epilepsy, as well as stimulating research in fundamental synaptic and cellular neuroscience.

Assessment of the team's organisation and life:

Nothing specific to mention.

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

Several masters and PhD students have been successfully trained.

Assessment of the five-year plan and strategy:

The team has a range of low- to high-risk projects. Among the projects that have the greatest potential impact is a concerted attempt to establish the mechanisms underlying different patterns of spontaneous activity that can occur both in ex vivo human brain slices and in intracranial recordings. The role of cholesterol metabolism in seizure-related cell death may be difficult to establish because of the abundance of other changes taking place. The work led by one team leader on presubicular neuronal properties could be strengthened by explicit hypotheses, as well as behavioural experiments. The human depth recordings do not provide compelling preliminary data to support a direct correlation with the rodent experiments on presubicular function. The project on imaging episodic memory appears disconnected from the rest. This is a highly competitive field, and the team may find it difficult to establish visibility in this area.

Conclusion:

- Strengths and opportunities:

Excellence in biophysics applied to epilepsy. The team takes advantage of proximity to a busy epilepsy surgery programme to understand ictogenic mechanisms, and this has yielded highly interesting results.

- Weaknesses and threats:

The publication record is patchy. There are concerns about succession because of the productivity of tenured researchers other than the senior team leader. Space constraints may make it difficult to accommodate additional researchers funded by the ERC grant.

- Recommendations:

The team should focus on its strongest areas. A solution must be found to ensure the team's viability beyond the retirement of the senior team leader. Failing this, the team could be merged with another one. A better integration needs to be found between clinical research, basic mechanisms and mathematical analysis.

4 • Team-by-team analysis

Team 11 : Optogenetic dissection of signal circuits underlying locomotion

Name of team leader: Ms Claire WYART

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	1	1	
N2: Permanent EPST or EPIC researchers and similar positions	1	1	
N3: Other permanent staff (without research duties)			
N4: Other professors (PREM, ECC, etc.)	1	1	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	7	
N6: Other contractual staff (without research duties)	2	1	
TOTAL N1 to N6	6	11	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	2	
Theses defended	0	
Postdoctoral students having spent at least 12 months in the unit	0	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	2	2

• Detailed assessments

Assessment of scientific quality and outputs:

This team was formed very recently with pump-priming from the ICM foundation and has received an ATIP/Avenir award. The team has a record of outstanding publications, including Nature with the team leader as a first author from her time as a postdoc, a Science coauthorship, and as a senior author in Nat Methods.

Assessment of the team's academic reputation and appeal:

The team leader receives many invitations to high profile international conferences. There are International collaborations with excellent groups. She received a starting ERC grant recognising her scientific potential, as well as funding from Fyssen and other French organisations.

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

The links to industry are existing but at an early stage.

Assessment of the team's organisation and life:

Ms Claire WYART has taken on duties in one of the translational platforms in addition to setting up zebrafish, automated motion analysis and running an independent team.

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

Involved in seminars for neurobiology for students (e.g. European meeting). The number of PhD and rotation students passing through the laboratory is impressive, reflecting the exciting technical advances and scientific questions being addressed.

Assessment of the five-year plan and strategy:

Several highly original topics are under investigation, including the role of interneurons in locomotion, the role of CSF contactng neurons, and technological developments in optogenetics. Very nice approach to the problem, using powerful experimental methodologies and highly sensible techniques to record in vivo the relevant elements of the analyzed system. Good knowledge of the limits of the problem and its potential importance. Young team with a very good program. Although established only a few years ago, this group has an excellent record. The potential for translation via an orthopaedic surgeon is relatively undeveloped at present

Conclusion:

- Strengths and opportunities:

Young team with a very good programme. Although established only a few years ago, this group has an excellent record. The expertise and access to very sensitive technologies are a powerful combination.

- Weaknesses and threats:

CSF contacting neurons are of unclear relevance to human pathophysiology. The relevance of the results for human health could be constrained. Analysis of this system in zebrafish could give relevant information for low vertebrates, but it may be vestigial in mammals.

- Recommendations:

To take full advantage of the environment it will be important to engage with mammalian models, and also to take a more integrative view of the segmental motor system that includes other inputs (lateral line system and vestibulo/reticulo spinal projections). Genetically encoded [Cl-] sensors may help test some of the hypotheses. The tasks of as the orthopaedic surgeon, with regards to the proposed clinical translation, will require detailed planning.

4 • Team-by-team analysis

Team 12 : Experimental neuro-oncology

Name of team leader: Mr Jean-Yves DELATTRE & Mr Marc SANSON

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	3	3	
N2: Permanent EPST or EPIC researchers and similar positions			
N3: Other permanent staff (without research duties)	3	2	
N4: Other professors (PREM, ECC, etc.)	1	1	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	5	9	
N6: Other contractual staff (without research duties)	7	3	
TOTAL N1 to N6	19	18	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	5	
Theses defended	0	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	3	3

• Detailed assessments

Assessment of scientific quality and outputs:

There is a very good level of publication, and many high profile papers in collaboration in international large genomics networks. Among the recent publications directly related to the proposed research programme and led by the team are a Lancet review, an article in Brain, several in J Clin Oncol, and an article (2007) and a letter in NEJM. In total 63 papers appeared in the last 3 years.

Assessment of the team's academic reputation and appeal:

This team is being led by Mr Marc SANSON with the retirement of Mr Jean-Yves DELATTRE. It is a widely recognised reference laboratory in the field of neuro-oncology and genomics, and is pursuing a good translational activity including a national referent tissue bank. Very good academic reputation in neuro-oncology. The senior team leader is on the editorial boards of leading oncology journals. The orther team leader is also recognised internationally.

The team coordinates 5 French programmes (1 on CNS lymphomas, 4 on gliomas), and receives INCa ARC funding. There are collaborations with French centres and with the Institute of Cancer Research, UK.

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

The team holds three patents on molecular markers. Team members are putting effort in in vitro/in vivo modelling of gliomas for targeted treatments (Gliotex project) with potential for industrial collaboration.

Assessment of the team's organisation and life:

The team has a good integration with the neurology department, with a good translational activity and interaction between clinical activity and research.

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

Several PhD and Masters students have been trained.

Assessment of the five-year plan and strategy:

The low-grade glioma project and the lymphoma projects are competitive. The Gliotex experimental therapeutics project is more preliminary. The research plan is clearly described. The molecular studies to redefine prognosis of gliomas have clear translational consequences. Translational activities and tumor bank are strong points of the team. Bioinformatics and cell biology could be strengthened. The Committee notes that several other teams could also benefit from stronger bioinformatics and cell biology.

Conclusion:

- Strengths and opportunities:

Strong translational activity, comprehensive tissue bank. The team has a very good expertise and ideal environment to develop the proposed programme.

- Weaknesses and threats:

The team would benefit from more bioinformatic expertise as well as more cell biology approaches. The identification of relevant cellular and molecular mechanisms in low grade gliomas remains incomplete. The strengths are in glioma prognosis and genetic pathways, and there is a risk that new projects (meningioma) could dilute the research focus.

- Recommendations:

The mechanistic work on cell signalling pathways could be strengthened. The team could seek to strengthen this area with a senior appointment.

4 • Team-by-team analysis

Team 13 : Mechanisms of myelination and remyelination in the central nervous system

Name of team leader: Ms Catheine LUBETZKI & Mr Bruno STANKOFF

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	2	3	
N2: Permanent EPST or EPIC researchers and similar positions	1	2	
N3: Other permanent staff (without research duties)	2	2	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	4	4	
N6: Other contractual staff (without research duties)	1	0	
TOTAL N1 to N6	**10**	**11**	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	1	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	3	4

• Detailed assessments

Assessment of scientific quality and outputs:

Both PIs have major contributions to the field in the last years, with 50 publications in the last 5 years in excellent neuroscience journals including Brain, Ann Neurol, PNAS. There is clear intellectual leadership by the team in approximately half of these papers.

Assessment of the team's academic reputation and appeal:

The team is internationally recognized in the field of myelin repair and the PIs are routinely invited to conferences worldwide. They are both members of several international expert committees and advisory boards in the field of MS. They hold French grants (ANR, ELA, FRM). Among the recent awards are the highly prestigious Sobeck prize for research in MS (Germany), and the NRJ-Fondation de France prize (Paris). They collaborate with groups in the UK, Canada, USA and Japan.

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

One team leader has been President of the French MS Society, and both PIs contribute to several other activities that raise awareness of MS and related disorders among the public. Both PIs consult for companies involved in MS therapeutics.

Assessment of the team's organisation and life:

Nothing specific to mention. The team appears to be run very efficiently.

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

Excellent activity: coordination of 3 Masters courses of UPMC and of the Medecine/Science programme.

Assessment of the five-year plan and strategy:

The two project lines focus on myelin repair mechanisms. One project includes original approaches to analyze the formation of nodes of Ranvier in "in vivo" myelin repair experiments, and transfection of bone marrow derived hematopoietic stem cells with oligodendrocyte progenitor guidance cues to improve remyelination. The other project centres on brain imaging to monitor demyelination with original tools (including PET), with a special emphasis on axonal signals and cortical demyelination (grey matter pathology). These represent powerful approaches to the problem, using modern exprimental methodologies and highly sensitive techniques in experimental models, whilst maintaining immediate translation relevance.

The further development of PET imaging in MS patients is a clear translational aspect of the research programme to improve diagnostic and prognostic markers for MS.

Conclusion:

- Strengths and opportunities:

Strong focus of the work programme on demyelination/remyelination in different in vitro and in vivo (animal) approaches and myelin imaging in experimental MS models and MS patients with a clear translational approach. Clear expertise and strong international acknowledge of leadership in the field. The proposal is innovative and represents a significant step forward in the group's scientific evolution. The group is leading the way in PET imaging in MS.

- Weaknesses and threats:

This is a highly competitive field. Development of new PET ligands is not considered.

- Recommendations:

Improved bioinformatics expertise could aid target selection in transcriptome analyses. The project on PET imagigng may benefit from engagement with experts in chemistry who may identify new candidate ligands.

4 • Team-by-team analysis

Team 14 : Functions and development of microglia

Name of team leader: Mr Michel MALLAT

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	0	0	
N2: Permanent EPST or EPIC researchers and similar positions	2	1	
N3: Other permanent staff (without research duties)	2	2	
N4: Other professors (PREM, ECC, etc.)	0	0	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	0	0	
N6: Other contractual staff (without research duties)	1	0	
TOTAL N1 to N6	**5**	**3**	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	2	
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit	0	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	2	1

• Detailed assessments

Assessment of scientific quality and outputs:

The Pi runs a small team, and is a recognised expert in microglia. The number of publications is not commensurate with the team's international profile and it is disappointing that no major papers have appeared since 2008 (J Neurosci).

Assessment of the team's academic reputation and appeal:

The group leader is widely recognised in the field of microglia development.

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

There is a collaboration on mobile phone radiation.

Assessment of the team's organisation and life:

This is a very small team in comparison with others in the Unit. Otherwise, nothing specific to mention.

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

Some of the researchers trained by the team have successfully gone on to gain international recognition in their own right and have formed their own team.

Assessment of the five-year plan and strategy:

The proposed research programme includes developmental aspects (role of microglia in astrogliogenesis) as well as the role of microglia in models of Alzheimer´s disease. These are potentially important areas given the increasing interest in the interface between inflammation and neurodegeneration, and related work is underway in teams 1 and 3. However, the microglial developmental program is the most promising given the team's expertise to date. The strategy to keep the team small is risky because of the difficulty of balancing collaborations with the core project.

Conclusion:

● Strengths and opportunities:

The team has an expertise in microglia, which is an increasingly important area of translational neuroscience. Availability of new tools to interfere with their function and development, including siRNA, are present.

● Weaknesses and threats:

Small team with low scientifc productivity. A grant expires in 2013 and the team may find it difficult to rebuild critical mass.

● Recommendations:

The team will need to make a decision whether to focus on intramural collaborations with other groups or to focus on its special area of expertise in microglial development. Merger with another team may be an option.

4 • Team-by-team analysis

Team 15 : Molecular and cellular approaches of myelin repair

Name of team leader: Mr Brahim NAIT OUMESMAR & Ms Anne BARON-VAN EVERCOORVEN

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	1		
N2: Permanent EPST or EPIC researchers and similar positions	3	3	
N3: Other permanent staff (without research duties)	2	2	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	10	11	
N6: Other contractual staff (without research duties)	1	1	
TOTAL N1 to N6	17	17	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	3	
Theses defended	4	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	3	2

• Detailed assessments

Assessment of scientific quality and outputs:

Both group leaders have major contributions to the field of myelin repair in the last years with several high-profile publications (JCI, PNAS, Brain, Stem Cells, JCB). They have also published in Nature Neurosci albeit not as corresponding authors. Among the advances from the team are new insights into oligodendrocyte precursor proliferation in models of inflammatory demyelination, and progress in harnessing Olig1/2 and tocopherol derivatives as potential therapeutic tools.

Assessment of the team's academic reputation and appeal:

Both PIs are internationally recognized and have excellent connections in the field of myelin repair, and PNS and CNS stem cells. Several international research programmes (NMSS, EU FP7). One Pi was president of the French Glial Club, and is associate editor of J Neurosci Res and member of the editorial board of Glia. Both PIs received awards from the NRJ. Both PIs are members of several expert and advisory boards/committees (ELA, French Ministry of Research concerning stem cells).

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

The team has built up contracts with Novartis, Korean Pasteur Institute, GyeongGi Bio-Center. The PIs present at patient support events.

Assessment of the team's organisation and life:

This large team (16 lab member, 5 permanent positions) appears to work remarkably smoothly.

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

Many students have been trained and now hold positions elsewhere.

Assessment of the five-year plan and strategy:

The project lines focus on transcriptional regulation of oligodendrocyte differentiation, stem cells/progenitor cells in myelin repair, and translational development of new therapeutics for remyelination. The work programme is clearly defined.

Conclusion:

- Strengths and opportunities:

Strong focus on myelin repair with a clear translational approach for an important disease area. Very good expertise and international recognition in the field. In particular, the team has demonstrated the ability to make progress from the fundamental mechanisms of oligodendrocyte precursor proliferation all the way through to identifying candidate therapeutic strategies.

- Weaknesses and threats:

The impending retirement of of one Pi will need to be managed without loss of productivity, because the team is large. Although the team has identified some candidate therapeutic strategies, a clear roadmap to clinical trials is lacking.

- Recommendations:

Appropriate delegation of leadership within the group may clarify the continuity and viability of each of the project experimental lines. The team should clarify how they will take their fundamental discoveries towards clinical trials.

4 • Team-by-team analysis

Team 16 : Development of oligodendrocyte and neurovascular interactions

Name of team leader: Mr Jean-Léon THOMAS & Bernard ZALC

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			
N2: Permanent EPST or EPIC researchers and similar positions	4	4	
N3: Other permanent staff (without research duties)			
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	5	
N6: Other contractual staff (without research duties)	2	2	
TOTAL N1 to N6	9	11	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	2	
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit	0	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	3	3

• Detailed assessments

Assessment of scientific quality and outputs:

Since 2007 there has been a substantial number of good publications in journals of medium impact. In most of these publications the leadership role of group PIs is clear. Publications have appeared in J Neurosci, Genes & Dev, Development. Among the advances are new understanding of how Hox homeoproteins affect oligodendrocyte development and remyelination, and the roles of VEGF and its receptors in adult neurogenesis.

Assessment of the team's academic reputation and appeal:

The group leader and the current head of the Center are internationally acknowledged experts in oligodendroglia. The team has attracted external grants (ANR, ARSEP) and have established international collaborations with excellent groups ouside the ICM.

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

The team has developped two patents.

Assessment of the team's organisation and life:

The succession following the former head of the team and unit retirement appears to be planned efficiently. Otherwise, nothing specific to mention.

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

Over the years, they have grown into a dynamic team, with a regular turnover of master's students, PhDs and postdoctoral fellows. Unit members are extensively involved in student evaluation committees.

Assessment of the five-year plan and strategy:

This team is developing a basic research program to understand fundamental aspects of glial cell biology in vertebrates. This includes a molecular and cellular study of oligodendrocyte progenitors and neural stem cells, using in vivo approaches to characterize the interaction of glial cells with their neural and vascular environment. Their investigations aim at identifying new signaling molecules in oligodendrocyte progenitors and neural stem cells, which could be applied to develop therapeutic tools regulating oligodendrocyte progenitors and neural stem cells in human CNS diseases. They are also generating new animal models for live imaging of myelin. These models are transgenic Xenopus which bring new insights on myelin development and myelin remodeling during lesion repair processes. Overall, the Committee considered this an important area, and the project on VEGF less well defined.

Conclusion:

- Strengths and opportunities:

The team has established a very broad range of experimental methods (molecular genetics, imaging, transcriptomic) and animal models (mice, chicken, Xenopus) for in vivo and in vitro investigations on glial progenitor/stem cells. The breadth, and in particular the Xenopus model, place the team in a strong position to compete internationally.

- Weaknesses and threats:

The team productivity could be higher. The translational component is not as strong as the Xenopus project. The VEGF area is a very competitive field and this part of the programme lacks a clear connection to the two first projects.

- Recommendations:

The xenopus part of the project is the most interesting, and deserving of more focus.

4 • Team-by-team analysis

Team 17 : PICNIC: Physiological Investigations of Clinically Normal and Impaired Cognition

Name of team leader: Mr Laurent COHEN & Mr Lionel NACCACHE

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	2	2	
N2: Permanent EPST or EPIC researchers and similar positions		1	
N3: Other permanent staff (without research duties)			
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	4	7	
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	6	10	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	5	
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit	4	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	2	3

• Detailed assessments

Assessment of scientific quality and outputs:

This group has made some important contributions to understanding cortical contributions to reading, attention and consciousness. All three PIs have delivered excellent research, with coherent plans, with a solid theoretical grounding and very good experimental techniques.A novel team member, who joined the group recently, has a long track record in behavioural studies of the neglect syndrome and more recently in tractography studies in patients (including a seminal study in Science). Another team member has made an impact in the field of consciousness, on his own and with collaborations with a Neurospin group outside ICM .

The group publishes well in high-impact general journals as well as in highly respected specialist journals in the field. Their papers have appeared in Science, PNAS, Neuron, PLoS Biology, Current Biology and Journal of Neuroscience.

Assessment of the team's academic reputation and appeal:

The group is world-leading in the field of reading and the role of the visual word form area. The team has an unusual if not unique identity. Its appeal lies in the fact that it is one of only a handful of research teams in the world with the capacity to explore its important questions of interest. All PIs have a clinical neurological background and have a strong interest in patient-related research, to inform both clinical and basic neuroscience questions.

The excellent quality of scientific work has been recognized with national and international prizes.

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

Team members have attempted to make innovative partnerships with research groups from different disciplines, including some focused on emerging high-tech solutions (e.g. Jerusalem group developing The vOICe, a device for blind people that might allow them to "see with sound" and the retinal prosthesis system being developed by Institut de la Vision). The potential for this programme of research to have societal impact is very good.

Assessment of the team's organisation and life:

Each section of the team has coherent and logical objectives. However, lack of a common space probably reduces interactions and cohesiveness between the groups. There are important overlaps between the behavioural, neuroimaging and neurophysiological methods used by all three PIs. They recognize the potential for collaboration and cohesion.

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

PIs teach clinical and masters students and supervise PhDs.

Assessment of the five-year plan and strategy:

The programmes of each of the PIs are original with innovation and evidence of risk-taking. Each has a program which appears to be of consistently high quality but some will take time to deliver because of the nature of patient-based research and the relatively small size of each group.

An important aspect of the strategy is to study neurological patients. In this respect, the team is highly unusual in the neuroscience field and shows some aspects of strong leadership in developing patient-based research. Critical mass might, however, be stronger in the future.

Conclusion:

- Strengths and opportunities:

Very strong, internationally recognized PIs, combination of impressive research work with clinical neuropsychology. Unusual and ambitious research programme, which has a strong patient-based approach. The group of PIs is of high quality and has great potential to deliver. It is ambitious and highly motivated. Excellent neuroimaging facilities.

- Weaknesses and threats:

No technical staff, and few researchers recruited recently. The 3 research lines are relatively independent, with more collaborations with other CRICM teams than within the team. Patient-related research can be extremely slow. To increase its impact in a clinical setting, wider clinical collaborations could help. The team's international profile may be lower than deserved because of its close alliance to NeuroSpin.

- Recommendations:

The committee encourages the team to continue with an outstanding research programme. The international visibility of the group might be improved with stronger links with groups outside France and stronger collaborations with groups who study similar patient cohorts. Critical mass of researchers would need to be increased to deliver with high impact.

4 • Team-by-team analysis

Team 18 : Cognition, neuroimaging and brain diseases

Name of team leader: Mr Bruno DUBOIS

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	2	2	
N2: Permanent EPST or EPIC researchers and similar positions	5	3	
N3: Other permanent staff (without research duties)	5	2	
N4: Other professors (PREM, ECC, etc.)		2	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	10	11	
N6: Other contractual staff (without research duties)	5	4	
TOTAL N1 to N6	27	24	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	7	
Theses defended	9	
Postdoctoral students having spent at least 12 months in the unit	4	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	5	2

• Detailed assessments

Assessment of scientific quality and outputs:

This is a large and highly successful group with strong links to clinical populations. They have published over 225 papers in the 5 year reporting period (2007-2012), including some in Brain, J Neurosci, PNAS , Neuroimage and Lancet Neurol.

Assessment of the team's academic reputation and appeal:

The team has substantial national and international grant income (3 ANR, 2 EU FP6, 3 PHRC, 3 NIH). The team also has a very high international visibility, with many invitations to conferences. They collaborate with international groups including a group at Harvard university. Team members sit on the INSERM Commission, AERES, the steering committee of National Alzheimer Plan and international bodies. To note, the team leader received the NRJ-Institut de France prize.

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

Some team members have strong visibility, delivering several talks to the general public and with high media presence. Three patents including one on tractography. Team members sit on the scientific board of 3 start-ups, and are past or present presidents or members of the Scientific committees of patient associations (Alzheimer, PSP, DFT, IFRAD).

Assessment of the team's organisation and life:

The team has re-structured on the basis of advice from the SAB last year. They have taken on board the suggestion to focus their research activity on a common goal. The organisation is now much more cohesive. The team is also involved in the research direction of IHU.

Assessment of the team's involvement in training through research

The team contributes extensively to teaching at UPMC. They have organised an International School, and a training course for high-potential executives (with IHU A-ICM & Collège des Ingénieurs). Seven current PhD students and 13 master students.

Assessment of the five-year plan and strategy:

The five-year plan and stratgey is very good. The team has re-focused its research on frontal lobe function localisation and definition of deficits related to different sub-regions. The new plan is articulated on four tightly interacting research lines, supported by good task designs and preliminary data.

Conclusion:

- Strengths and opportunities:

The research programme of the team is tightly integrated, with four interweaving themes, led by the junior Pis. They have important toolbox of techniques, including original methodological developments (e.g. tractography). The tasks have already been defined for the projects, and preliminary data are available, lending credibility to the projects. Integration between theory and scientific/clinical research. The team has ready access to large patient cohorts. Possibility of synergy with another leading group on PFC research at Ecole Normale Supérieure Paris.

- Weaknesses and threats:

High clinical workload for many staff members. Some of their projects using patient cohorts may be difficult to interpret; there are possibilities of confounds that might render interpretation complex. Not strong on mechanistic neurobiological or computational hypotheses. The insights that can be derived from DTI are not clear.

- Recommendations:

The team should consider integrating MEG and surface EEG. Also, they should consider collaboration with or integrations of researchers developing mechanistic neurobiological or computational hypotheses.

4 • Team-by-team analysis

Team 19 : Social and Affective Neuroscience

Name of team leader: Ms Nathalie GEORGE

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		1	
N2: Permanent EPST or EPIC researchers and similar positions	3	2	
N3: Other permanent staff (without research duties)	3	2	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	8	
N6: Other contractual staff (without research duties)	2		
TOTAL N1 to N6	9	13	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	6	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit	0	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	1	3

• Detailed assessments

Assessment of scientific quality and outputs:

This is a relatively new team, which has yet to gain widespread recognition. The quality of research is good and there is evidence of ambition to go further, albeit within a relatively narrow framework of affective and social interaction influences on perception.

The group has ambitions to make a contribution to understanding anhedonia and depression, two important conditions that have an important societal and economic impact. It has begun to position itself to apply basic neuroscience methods to these syndromes. There is a steady rate of publication in specialist journals (Cerebral Cortex, Neuroimage).

Assessment of the team's academic reputation and appeal:

The team has a very good academic reputation, as witnessed by membership of the Editorial Board of Neuroimage. The team publishes in good international journals but its contributions would have greater significance if some of their studies could be published in higher impact journals. The team holds a number of grants from the ANR and has received some European funding.

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

They have developed a potentially important partnership with a pharmaceutical laboratory to study the effects of agomelatine (Valdoxan, a melatoninergic agonist and 5-HT2C antagonist). The team also has an innovative partnership with RATP (Régie Autonome des Transports Parisiens) to study emotional reactions to passenger density.

Assessment of the team's organisation and life:

The team appears well organized and has coherent and logical objectives.

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

The group leader and staff teach masters and clinical students.

Assessment of the five-year plan and strategy:

The overarching program is original with innovation and evidence of risk-taking. In general this is an ambitious program but perhaps the theoretical underpinnings could be more robust. The justification for much of the work on influences of affective state on perception is that this is part of a loop that perpetuates depression. The team have not put as much effort into considering underlying mechanisms more deeply. One important aspect of the strategy is to leverage basic neuroscience findings to the clinical setting. In this respect basic neuroscience group is very unusual and has the potential to make an impact in neurological and psychiatric conditions.

Conclusion:

- Strengths and opportunities:

Interesting research program in a developing area of basic neuroscience, which has potential for application to brain disorders. The group of PIs is of high quality and has potential.

- Weaknesses and threats:

In general, the theoretical underpinnings of the program need to be strengthened. There is a lack of critical mass. Furthermore, to make an impact in the clinical setting, it would be important for the group to interact more widely with clinicians. If this does not happen there is a potential threat to any translational ambitions.

- Recommendations:

The team could improve theoretical basis of current plans focusing more on mechanisms. They may develop deeper, hypothesis-driven projects. The critical mass of researchers would need to be increased to deliver with high impact. The visibility of the team could be improved with enhanced international collaborations, for example on the topics of anhedonia and depression.

4 • Team-by-team analysis

Team 20 : Behavior, emotion, and basal ganglia

Name of team leader: Mr Luc MALLET

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			
N2: Permanent EPST or EPIC researchers and similar positions	2	2	
N3: Other permanent staff (without research duties)			
N4: Other professors (PREM, ECC, etc.)		1	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	2	
N6: Other contractual staff (without research duties)	1	1	
TOTAL N1 to N6	4	6	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	3	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	0	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	2	2

• Detailed assessments

Assessment of scientific quality and outputs:

The team published a very important first author paper in N Engl J Med in 2008, which reported on the effectiveness of high-frequency STN stimulation in refractory OCD. In addition to that paper they have published in Brain, Arch Neurol, and Neuroimage. The team contributed to the identification of electrophysiological and metabolic predictors of stimulation efficacy, and one team member created a deformable histological atlas of the human brain that is now the basis for preoperative targeting procedures in functional neurosurgery, at the Pitié-Salpêtrière as well as other teaching hospitals in France.

Assessment of the team's academic reputation and appeal:

The team has an international profile in the role of the STN in OCD. The Committee noted that it will move to another research centre in the Paris area in the next few years. This presumably reflects the prospect to give added value to the academic psychiatry community there. Although this would be a loss to the CRICM the case for such a move is strong because it would offer access and proximity to patients.

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

The team has demonstrated interactions with the French OCD patients association (AFTOC), and have provided educational software for patients and the general grand public. The team has an industrial partnership.

Assessment of the team's organisation and life:

The team have successfully managed the succession of the previous leader. Otherwise, nothing specific to mention.

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

The team is involved in teaching at the Univ Paris 6 (UPMC). They specifically participate in the training course for high-potential executives (with IHU A-ICM & Collège des Ingénieurs); Over the last years, the team successfully trained 3 PhD students.

Assessment of the five-year plan and strategy:

The focus is relatively narrow (STN in OCD) although there is a very ambitious programme of research. The main objective of the the first project is to investigate the role of basal ganglia circuits in normal and pathological behaviours by combining purpose-built behavioural tasks to behavioural, neuroimaging and electrophysiological recordings. They propose to study the reciprocal influences of emotional versus motor contexts in OCD, dystonic and Tourette syndrome patients by using the emotional categorisation task. Then, they plan to investigate how and where in the cortical-subcortical circuitry emotional and motivational information influence perceptual decisions. The project 2 is a natural continuation of the successful BG atlas in combination with functional and interesting 7T tractography studies, and this is likely to yield important results. The objective of project 3 is to develop new experimental therapeutics, starting with the development of rodent and non-human primate models of OCD and cocaine addiction. These models will be used to study the clinical effects of subthalamic DBS and its mechanisms. The animal studies will rely on a young researcher who has recently joined the team, but will also benefit from collaboration with a group in Lyon) and another one in Marseille.

Conclusion:

- Strengths and opportunities:

The team has built a recognised expertise in a relatively narrow area, which constitutes an obvious strength.

- Weaknesses and threats:

It may be difficult to recruit a large number of subjects. In addition, with only one mouse model it may be difficult to validate its relevance to the human condition. The move to another research center will need to be managed without detriment to the research. The programme of research is ambitious and seems disproportionate to the publication record.

- Recommendations:

The team is encouraged to collaborate with other teams overseas since it may allow more patients to be studied.

4 • Team-by-team analysis

Team 21 : Motivation, brain and behavior

Name of team leader: Mr Mathias PESSIGLIONE

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			
N2: Permanent EPST or EPIC researchers and similar positions	1	1	
N3: Other permanent staff (without research duties)			
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	5	12	
N6: Other contractual staff (without research duties)	1		
TOTAL N1 to N6	7	13	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	5	
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit	0	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	1	1

• Detailed assessments

Assessment of scientific quality and outputs:

This is an impressive teamgroup of young investigators who are original and ambitious in the scope of their research. The group leader has already gained international recognition in the field of motivation, reward and neuroimaging, with some very high profile publications. The other two researchers also have very good to excellent records for their career stage, one being highly competent in computational modelling, while the other brings rare expertise in recording from awake behaving monkeys. The group leader has, in particular, led some innovative and important work on the effects of subliminal stimuli on behavior. The papers from the team have appeared in high-impact general journals as well as in highly respected specialist journals in the field: Neuron, Journal of Neuroscience, Neuroimage, Brain and J Neurophysiol.

Assessment of the team's academic reputation and appeal:

The team has already achieved a very good academic reputation. This is particularly through the visibility of its senior member, who has received an ERC grant.

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

Team members have been highly original in the methodology they have used to investigate effort, value and reward representations within the brain. They have been particularly innovative in trying to produce partnerships with neurologists and psychiatrists. The potential for this program of research to have societal and economic impact is huge.

Assessment of the team's organisation and life:

Currently there is only one tenured staff member. The team are at an early stage of pursuing partnerships with neurologists and psychiatrists. There is evidence of cross-cutting scientific coordination across the human behavioural, neuroimaging, monkey physiology and computational objectives of the group.

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

The team has trained several masters students, while the number of trained PhD students is still small, explained by the short history of the team. The team staff has organised training workshops.

Assessment of the five-year plan and strategy:

The overarching program is highly original with evidence of risk-taking, which is to be commended at this stage of their careers. In particular, the reinforcement learning work is starting to develop a momentum of its own. The predictive utility of dynamic causal modelling is at present untested, and this part has yet to emerge from the shadow of a former PI. Some of the non-human primate project is at present only seeking validation in relation with the human imaging, but in the long term this may be a very important arm to the collaboration.

Conclusion:

- Strengths and opportunities:

The research programme is ambitious and unusual in an important area of basic neuroscience which has quite deep implications for understanding and treating brain disorders. The team is of high quality and has great potential to deliver. The team is ambitious and highly motivated. In addition, the international collaborations are of very high level.

- Weaknesses and threats:

Only the group leader has security of tenure. To take full benefit from the team setting, it is important for the team to interact more closely with clinical colleagues. If this does not happen there is a potential threat to the long-term translational ambitions of the program.

- Recommendations:

The team should strengthen collaborative projects. The team should also seek international partners in clinical projects to increase impact and tempo of patient studies.

4 • Team-by-team analysis

Team 22 : ARAMIS: Algorithms, models and methods for images and signals of the human brain

Name of team leader: Mr Olivier COLLIOT & Mr Didier DORMONT

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	4	4	
N2: Permanent EPST or EPIC researchers and similar positions	3	3	
N3: Other permanent staff (without research duties)	8	7	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	4	12	
N6: Other contractual staff (without research duties)	15	9	
TOTAL N1 to N6	34	35	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	7	
Theses defended	5	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	4	4

• Detailed assessments

Assessment of scientific quality and outputs:

This team provides a large variety of basic methodological infrastructure. It has quite diverse interests in image analysis, and has contributed to a very substantial number of high-quality publications, although in many cases as middle authors. However, team members also have a good number of first and last author papers in high quality specialist imaging journals (e.g. IEEE and Neuroimage). Many aspects of their work are highly original and the scope of their research is quite ambitious. They have made some important contributions to several fields, including the development of automated methods for measuring brain regions and connections. The functional imaging work is less well developed but the team clearly recognise the opportunities to push forward with integration of multiple imaging modalities.

Assessment of the team's academic reputation and appeal:

The team has a high-profile position in France and internationally. Team members have many international collaborations. The group is part of the Centre for Image Acquisition and Processing (CATI). This is an important joint partnership with several other institutes including Neurospin. It is part of an ambitious project to build a national infrastructure for multicentre studies in Alzheimer's disease (for example the MEMENTO national cohort in France). They also made good partnerships with basic cognitive neuroscientist with respect to MEG methodology. These developments have led to impact in the international and scientific community. The team has applied for membership of INRIA (the National Institute for Informatics Research).

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

They have made partnerships with clinicians, particularly in the fields of dementia and epilepsy research. Several patents are held by the team and one has been commercialised (Neurinfarct).

Assessment of the team's organisation and life:

The team has a large and complex structure including many researchers with a computational and physical background. They have successfully managed to preserve an identity within the Unit.

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

The team is involved in successfully training Masters and PhD students.

Assessment of the five-year plan and strategy:

The team has an ambitious plan to push the resolution of structural imaging, integrate post-mortem data, and develop algorithms to apply deformation mapping to diffusion imaging and tractography. The longitudinal imaging work will also potentially lead to important advances. It is more difficult to evaluate the likely success of the graph theory and brain-computer interface work, which are both fashionable areas.

Conclusion:

- Strengths and opportunities:

The team has access to data from 7T scanner (at NeuroSpin), MEG, large subject cohorts, and benefit from excellent integration in national and international structures. The team also reach a critical mass of researchers. This is undoubtedly a strong methodological group which has great opportunities through its links with clinical populations and its partnerships with national excellence centres. It has a real opportunity to contribute at the very highest levels internationally. The multidisciplinary nature of the group members provides a highly unusual and strong base for further development.

- Weaknesses and threats:

The group members appreciate that the diverse nature of their project's risks possible dilution and loss of focus but, given strong leadership, there is the possibility of keeping the programme on course.

- Recommendations:

Build on existing strengths and opportunities.

4 • Team-by-team analysis

Team 23 : Biotechnology and biotherapy

Name of team leader: Mr Philippe RAVASSARD

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	1		
N2: Permanent EPST or EPIC researchers and similar positions	2	2	
N3: Other permanent staff (without research duties)	4	3	
N4: Other professors (PREM, ECC, etc.)			
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	4	7	
N6: Other contractual staff (without research duties)	9	7	
TOTAL N1 to N6	20	19	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	1	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	0	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	2	2

• Detailed assessments

Assessment of scientific quality and outputs:

This is an unusual team that balances many service commitments (production of lentiviral vectors, supervision of the animal house, biotech spinoff) with its own research agenda. The scientific output has been diverse, and reflects in part the legacy of a former team leader:

- Refinement and validation of a rodent model of schizophrenia,

- Method refinement in transgenic mouse production with lentiviral vectors,

- Epigenetic mechanisms of early life nutritional programming,

- Generation of a human pancreatic beta cell line that retains glucose-dependent insulin secretion,

- Characterisation of long non-coding RNA (lncRNA).

Most of the papers have arisen from collaborations. Relatively few paper have been signed as first or last authors by present team members. A high-profile paper in JCI (2011) was published in collaboration with an investigator from Necker. This, and another paper in Cell Metab, is more relevant to meabolic disease than the main focus of the Unit.

Assessment of the team's academic reputation and appeal:

The team has coordinated or participated in a large number of research collaborations, including seferal EU grants as well as an NIH grant. The group leader is member of the Beta Cell Biology Consortium (BCBC) the major NIH founded consortium in the US in the field of diabetes.

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

Team members have developed tight links with non-academic partners. They have two research contracts with a pharmaceutical company, contracts with four big pharmaceutical companies in the context of the IMDIA consortium. Several patents are held by the team, including one on a human beta cell line, which has been commercialised by a spin-off company (Endocells, founded by the group leader), which is on the ICM site. Other patents concern methods of producing human beta cell lines and lentiviral vectors allowing RNAi mediated inhibition of GFAP and Vimentin expression, as well as a patent on RNAi mediated expression inhibition of a cholinergic protein. Another spin-off company, was founded by a former group leader.

Assessment of the team's organisation and life:

The team have successfully managed a complex interaction of service, collaborative research and commercial contracts. Otherwise, nothing specific to mention.

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

The team trained 5 PhD students and several masters students over he past. The group leader is responsible for the human genetics module in an engineering school and teaching in regenerative medicine at the Free University of Brussels (Belgium).

Assessment of the five-year plan and strategy:

Among the diverse objectives and projects the lncRNA work is potentially the most promising and deserves investigation as a new class of genomic regulators. Although there is circumstantial evidence that lncRNA plays roles in CNS development and neurodegenerative disease the team is currently only pursuing its role in pancretive beta cells. Although the team is successful in various methodological developments the overall impression is that it is not well aligned with the research priorities of the Unit as a whole.

Conclusion:

- Strengths and opportunities:

The team is enthusiastic and creative, with access to state of the art facilities.

- Weaknesses and threats:

Much of the research work appears to be driven by seredipitous discovery rather than by an overarching goal of understanding an aspect of CNS function. Lack of identifiable leadership in projects that go beyond methodological advances to understand normal physiology, disease mechanisms or test novel therapies. There is a risk that the team may act as the R&D department of the spin-off company (Endocells).

- Recommendations:

The team should consider collaborating with one or other team in the Center to apply their powerful molecular tools to an aspect of neurological disease or brain/spinal cord function.

5 • Conduct of the visit

Visit dates:

Start: 21 January 2013 at 8h50

End: 23 January 2013 at 15h00

Visit site(s):

CRICM

Address (no. street town):

Campus La Salpétrière 75006 Paris

Conduct or programme of visit:

Monday 21st January

8.45 AERES coordinator to committee

9.10 Current Director presentation: B. ZALC

9.30 Income Director presentation: A. BRICE

10.10 IHU/ICM Director presentation: B. FONTAINE

10.45 Thematic axes presentation

11.45 Core facilities presentation: CENIR-IRM, CENIR-MEG, CIC, PICPS, BioCollections, Animal Core Facility

13.15 Lunch with Team Leaders

14.30 Team presentations :

Two parallel subcommittees

(20 min presentation, 20 min questions, 5 min discussion behind closed doors)

Time	***Team***	***Experts***	***Team***	***Experts***
14.30	EQ 1.: S. BOILLÉE	SCHWAB, BRÜCK, FINOCCHIARO, MARTINEZ, BERGER, BUÉE, VIVIEN	EQ6 : A. BACCI	TAMAS, BERNARD, HUSEIN, BATTAGLIA, BENAZZOUZ, KULLMANN
15.15	EQ2 : A. BRICE	SCHWAB, BRÜCK, FINOCCHIARO, MARTINEZ, BERGER, BUÉE, BENAZZOUZ	EQ7 : S. CHARPIER	TAMAS, BERNARD, VIVIEN, HUSEIN, BATTAGLIA, KULLMANN
16.00	EQ3 : S. HAÏK & M.C. POTIER	FINOCCHIARO, BERGER, BUÉE, BENAZZOUZ, VIVIEN	EQ8 : B. FONTAINE & S. NICOLE	TAMAS, BERNARD, HUSEIN, BATTAGLIA, MARTINEZ, BRÜCK, SCHWAB, KULLMANN
16.45	*Short Break*			
17.00	EQ4 : E. HIRSCH	BUEE, Benazzouz, HUSEIN, BATTAGLIA, VIVIEN, BERGER	EQ9 : E. LEGUERN & S. BAULAC	BERNARD, TAMAS, SCHWAB, MARTINEZ, BRÜCK, FINOCCHIARO, KULLMANN
17.45	EQ5 : M. VIDAILHET & S. LEHÉRICY	BUEE, BENAZZOUZ, HUSEIN, BATTAGLIA, VIVIEN, MARTINEZ	EQ10 : R. MILES & D. FRICKER	BERNARD, TAMAS, BERGER, SCHWAB, BRÜCK, FINOCCHIARO, KULLMANN

Tuesday 22nd January

8.45 Arrival on site

9.00 Team presentations :

Time	***Team***	***Experts***	***Team***	***Experts***
9.00	EQ17 : L. COHEN & L. NACCACHE	HUSSEIN, BATTAGLIA, BUÉE, BENAZZOUZ, BERGER, FINOCCHIARO	EQ11 : C. WYART	BERNARD, TAMAS, VIVIEN, SCHWAB, MARTINEZ, BRÜCK, KULLMANN
9.45	EQ18 : B. DUBOIS & R. LEVY	HUSSEIN, BATTAGLIA, BERNARD, TAMAS, Benazzouz, KULLMANN	EQ12 : M. SANSON	BERGER, FINOCCHIARO, BRÜCK, MARTINEZ, VIVIEN, SCHWAB, BUÉE
10.30	EQ19 : N. GEORGE & Ph. FOSSATI	HUSSEIN, BATTAGLIA, BERNARD, TAMAS, KULLMANN	EQ13 : C. LUBETZKI & B. STANKOFF	BRÜCK, MARTINEZ, VIVIEN, SCHWAB, FINOCCHIARO, BERGER, BUÉE, BENAZZOUZ
11.15	*Short Break*			
11.45	EQ20 : L. MALLET	HUSSEIN, BATTAGLIA, BENAZZOUZ, BERNARD, TAMAS, KULLMANN	EQ14 : M. MALLAT (microglia)	BRÜCK, MARTINEZ, VIVIEN, SCHWAB, FINOCCHIARO, BERGER, BUÉE
12.30	EQ21: M. PESSIGLIONE & J. DAUNIZEAU & S. BOURET	HUSSEIN, BATTAGLIA, BENAZZOUZ, BERNARD, TAMAS, KULLMANN	EQ15: B. NAIT OUMESMAR & A. BARON VAN EVERCOOREN	BRÜCK, MARTINEZ, VIVIEN, SCHWAB, FINOCCHIARO, BERGER, BUÉE

13.15 Lunch with team leaders and associated investigators

14.30 Team presentations :

Time	***Team***	***Experts***	***Team***	***Experts***
14.30	EQ22 : O. COLLIOT & D. DORMONT	HUSSEIN, BATTAGLIA, BENAZZOUZ, BERNARD, TAMAS, KULLMANN	EQ16 : J.L. THOMAS & B. ZALC	BRÜCK, MARTINEZ, VIVIEN, SCHWAB, FINOCCHIARO, BERGER, BUÉE
15.15	EQ23 : Ph. RAVASSARD	BERNARD, TAMAS, BRÜCK, MARTINEZ, VIVIEN, SCHWAB, FINOCCHIARO, BERGER, BUEE, KULLMANN		

16.00 Parallel meetings with:

Scientific staff (permanent scientists without team leaders) (Room n° 4)

Technical staff (Auditorium)

Students and Postdocs (Room n° 1/2)

17.00 Closed committee discussion

17.45 Interview of the current director (Mr Bernard ZALC)

18.30 End of day 2

Wednesday 23rd January

8.45 Arrival on site

9.00 Interview of the income director (Mr Alexis BRICE)

9.45 Closed discussion (report)

12.30 Lunch with institution representatives

13.30 Closed and final discussion

14.30 End of the visit

Specific points to be mentioned:

Two of the committee experts, Mr Gabor TAMAS (Hungary) and Mr. Francesco BATTAGLIA (Holland), were blocked in airports due to a major snowstorm over Europe on Sunday 20th of January and couldn't join the evaluation.

6 • Statistics by field: SVE on 10/06/2013

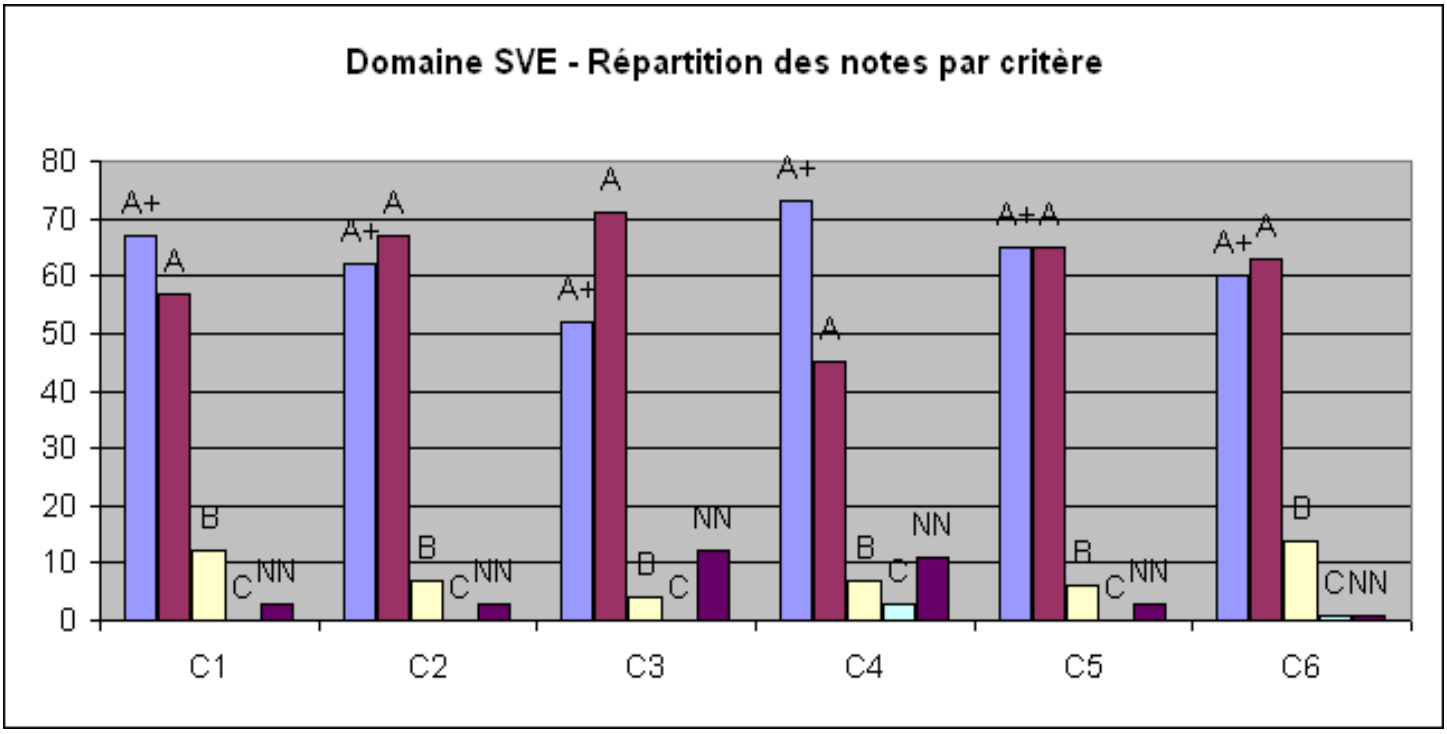
Grades

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

Percentages

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%

Histogram



7 • Supervising bodies' general comments

Paris le 26 04 2013

Le Président
Didier Houssin
Agence d'évaluation de la recherche
et de l'enseignement supérieur
20 rue Vivienne - 75002 PARIS

M. le Président,

Nous avons pris connaissance avec le plus grand intérêt de votre rapport concernant le projet de l'Institut du Cerveau et de la Moelle épinière (ICM), porté par M. Zalc. Nous tenons à remercier l'AERES et le comité pour l'efficacité et la qualité du travail d'analyse qui a été conduit.

Ce rapport a été transmis au directeur du laboratoire qui nous a fait part en retour de ses commentaires que vous trouverez ci-joint. Nous espérons que ces informations vous permettront de bien finaliser l'évaluation du laboratoire.

Restant à votre disposition pour de plus amples informations, je vous prie de croire, M. le Président, à l'expression de mes salutations respectueuses.

Le Vice -Président Recherche et Innovation

Paul Indelicato

Vice-présidence Recherche et Innovation
Tél. 01 44 27 20 09
www.upmc.fr

cricm
centre de recherche
de l'institut du cerveau
et de la moelle épinière

Response to the AERES report concerning the renewal of research center of the ICM (INSERM, CNRS and UPMC)

Paris, le 16 avril 2013

www.cricm.upmc.fr

N. Réf : AB/ND/1604

V. Réf : D2014-EV-0751722P-S2PUR140005711-002501-RT

The AERES report has been examined by the team leaders and the direction of the institute.

Our observations are enclosed comprising a number of factual errors and our response to specific comments.

We wish to thank the committee for his review of our institute and the useful comments.

Professeur Alexis Brice
Future Director

Centre de Recherche UPMC/Inserm UMR-S 975/CNRS UMR 7225
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General observations on the report of the AERES Committee

2. General assessment of the unit (page 6)

"The scientific teams are, to a certain extent, continuing to work in relative isolation from one another:" The recent move into the ICM building (2011) has provided an appropriate geographical context that will increase interactions among the teams. In addition, we have rejuvenated axis leadership and encouraged the organization of regular axis seminars and meetings for the discussion of progress reports, potential collaborations and shared applications for funding. . In fact, several of these collaborations are already fruitful as illustrated by the recently published paper in Nature Genetics, which results from the collaboration of 3 teams in the ICM (see comment by team 9). This is medium and long term strategy has already increased interactions but needs to be further developed.

"*The Unit does not have world-class bioinformatics on site:*" This was a clear need for many of the teams. Fortunately, with the support of the IHU-A-ICM program, we have just hired Dr. Ivan Moszer (former head of Bioinformatics at the Pasteur Institute) who is setting up a bioinformatics and biostatistics platform devoted to research and service to the teams. He has already recruited two bioinformaticians and obtained funding from the IHU-A-ICM for several more.

"*Some of the teams that have previously been very successful in identifying genes appear to be experiencing difficulties in making an impact in studying the molecular and cellular mechanisms downstream from the mutations:*" This is an important goal for translational research. Several of these teams have already invested this field and recruited experts in cell and/or molecular biology. The time frame of this research is longer term, and important results should be obtained before the next evaluation. In addition, the unique combination of teams with clinical and basic research skills should allow the development of multidisciplinary approaches.

" *The Committee considers it important that the Unit formulates a medium to long-term strategy to focus recruitment of new teams and management of existing teams that may require reconfiguration to improve synergies of the existing expertise:*"An international call for new team leaders will be launched jointly by the ICM and the IHU-A-ICM in April 2013. As a result of our reflections on strategy and with the advice of our SAB, we have identified 3 areas that we would like to reinforce: cell biology of neurodegenerative disorders, neuroimmunology, modelisation of behavior and diseases. In addition, following the team by team analysis performed by the AERES committee, we envision reconfiguration of several teams and have begun discussions with the corresponding team leaders. The public and private supervising bodies will be implicated in these decisions.

"*If the unit decides to commit to clinical trials it will require the establishment of a clinical trials office and academic appointments in the evaluation of outcomes:*" Since the CIC (center for clinical investigation), located within the ICM building and headed by JC Corvol, was not evaluated concomitantly with the unit, we probably have not insisted enough on the large number of clinical trials already performed in the Institute and the

hospital by our researchers. In particular, the CIC, which was recently evaluated by the AERES, has approximately 50 ongoing protocols involving researchers of the Institute. The CIC provides support for investigators not only in the performance of the studies but in the methodology. The CIC is complemented by the related CET (center for experimental therapeutic trials) in the Neurology Department. The latter is supported by the IHU-A-ICM and aims at facilitating trials that do not require a high level of technicity (i.e. cohort follow-up). Both structures provide very useful facilities and resources for clinicians working on translational neuroscience projects. Nevertheless, the major problem we are facing is the length of time it takes to promote the studies and obtain the legal authorizations. We have planned to hire a project manager in partnership with Inserm (our major promotor for physiopathological and cognitive research) in order to improve our applications to the different administrative bodies and reduce the administrative delays.

3. Detailed assessments (pages 7-8)

"*The complex relationship between the ICM foundation, CNRS, INSERM and University has generally been managed successfully, although the governance structure is not fully transparent to some junior researchers and technical and engineering staff*:" We recognize that governance has been quite complex because of the superposition of independent structures and that this situation called for simplification. As explained in our written document and oral presentation, the governance of the future research center of the ICM and the ICM Foundation will be unified as of January 2014, as part of a plan of convergence agreed to by all of the supervising bodies.

" *The Committee also heard that there was insufficient clarity regarding such matters as criteria for promotion and bonuses for technicians and engineers*:" The criteria for promotions and bonuses for technicians and engineers are regularly discussed with team leaders and platform scientific directors (Team Council) and also with elected representatives of the different categories of the unit staff (Staff Council). In addition, a local committee comprising team leaders and/or platform scientific directors assists the management team in making decisions about promotions. The Staff Council is informed and consulted and its resolutions are communicated to all staff members. Since 2009, 24 engineers and technicians of the Institute have been promoted.

"*The committee heard that relatively few students are going to international and national meetings, with haphazard access to support for travel and registration:*" ICM policy is that each PhD student should be able to attend (and present his work) at least one national and one international congress during his PhD studies.

"*The unit is also somewhat remote from some of the world-class science in related disciplines elsewhere in the Paris area*": Individual teams at the ICM with many of the teams working in the field of Neuroscience in the Paris area (e.g. Institut Pasteur, Institut du Fer à Moulin, Institut Alfred Fessard, campus Jussieu, Site des Saints-Pères, Neurospin, etc). In addition, the ICM participates in several schools, foundations, laboratories and infrastructures of excellence, including one or more of these Institutes, several of which were created by the recent initiative for excellence (e.g. Labex Bio-Psy, Paris School of Neurosciences – ENP, Fondation Fondamental, Neuratris, France Live

Imaging, Infrastructure des Biobanques, etc). Taking the ENP as an example, 21 teams of the ICM have been elected members of the ENP and 2 of our senior staff scientists have been nominated in the ENP council.

"The unit's strategy is relatively unfocused at present. It cannot cover comprehensively the entire area of basic and translational neuroscience. The priority at present appears to be the recruitment and consolidation of researchers who publish successfully. This may be a sensible 'hands off' approach to allow the Unit to attain a high level of international visibility, but it does not necessarily take advantage of the unusual location and intimate relationship with the Pitié-Salpêtrière hospital to maximise the potential translation of discoveries for patient benefit:" Our objective is not to cover the entire field of neuroscience; we have already focused our efforts on 4 scientific and medical axes, plus a methodological axis; many areas of neuroscience are not covered by the Institute. Our strategy is to reinforce these axes, in particular by recruiting teams that will provide expertise that is deemed to be missing (see above the international call for new team leaders). New teams will be recruited on the basis of both their scientific excellence and the priorities defined in the call, as well as their ability to interact with existing teams in a collaborative spirit. We are aware of the strength represented by the clinical neurosciences at the Pitié-Salpêtrière Hospital, and many of our investigators are MDs attached to the hospital and/or the medical school. This creates a true continuum between basic and more clinical research, and facilitates the development of high level translational research. However, we feel that the best translational research cannot be achieved without a strong foundation in basic research. This is why our Institute mixes together teams with more clinical or more basic approaches.

4. Team by team analysis

We thank the AERES committee for its analysis and advice. Most of the teams felt that their evaluations did not need further comments or responses. Others, however, wished to clarify some aspects of their research projects.

Team 1 (Séverine Boillée, pages 9-11)

"Assessment of the five-year plan and strategy"
Concerning the iPS cell bank and the sentence *"It is not clear to the committee how large this bank would be and what its availability would be to external users:"* Our aim is to make iPS cells from up to 30 ALS patients. This will include patients carrying mutations in C9ORF72, SOD1, TARDBP or FUS (at least 2 patients per gene), families with still undiscovered novel causative genes and 3 sporadic ALS cases. Under non-competitive agreements, all these iPSc will be made available for collaborations.

"Some of the proposed experiments have already been partially published by other teams (Liu, 2012, Am J Neurodegen, and Fiala, 2010, J Neuroinflammation, with a microarray exploring 28.869 genes). "This is a competitive area": The two papers quoted, both from the same group, studied the influence of exogenous aggregated SOD1 in vitro on mixed blood mononuclear cells (PBMCs) from ALS patients. With this approach they obtained RNA profiles mainly of sporadic ALS patients. Our project has a different aim. We are

focusing on the role of peripheral macrophages along affected peripheral nerves compared to central microglia in the affected spinal cord during the disease course in ALS mice. The animal model will be compared to patients with familial forms of ALS caused by different ALS-linked gene mutations using peripheral nerves from autopsies and defined macrophage populations either from blood or iPSc. We believe that our approach is sufficiently incisive to lead to novel insights.

"Conclusion"
"*This is a competitive area of research and other models of C9orf72 are being developed*" and "*Some other teams are working on overlapping topics:*" We are aware that most of the ALS teams worldwide are undertaking projects on the C9ORF72 gene. Our models include iPSc (see above) and mice. We use two approaches: i) the development of stable lines as part of a consortium; ii) the use of lentiviral transgenesis that is less time and cost consuming. Our work overlaps with that of Team 2, which has expertise on Frontotemporal degeneration (FTD) complementary to our expertise on ALS. Some of our team members already collaborate closely with members of Team 2 on the genetics (leading to 5 publications) and neuropathology of the disease. We believe that combining our complementary approaches will rapidly lead to a better understanding of C9ORF72-linked pathology.

Team 3 (Stéphane Haïk and Marie-Claude Potier, pages 15-17)

We thank the committee for the valuable review of the team and for their recommendations that we will carefully take into consideration. We wish to comment on two points mentioned as weaknesses and threats in the report.

"*The projects on prions are high risk:*" research on prions in Alzheimer's disease might be considered of high-risk because of its originality in an area that has emerged only recently in the field of neurodegeneration. We would like to point out, however, that this research is based on solid on-going clinico-pathological and basic prion research that has been validated by "a steady output of publications" (Ann Neurol and Hum Mol Genet mentioned by the committee, but also Lancet 2010 and J Virol 2013), by substantial and sustained funding obtained from various French agencies, EU and industry as indicated in the committee report itself and by recognized expertise (the team coordinates the National Center of Reference for Prions and the National Surveillance Network for CJD, is part of a JPND-Consortium and the Euro-CJD Network, and actively collaborates with equivalent national structures from the USA, UK, Germany and Italy).

"*In vivo imaging of A-beta is a competitive area*": We fully agree with this remark, but would like to mention that our on-going project of imaging in AD not only detects amyloid pathology in vivo but also tau pathology using original antibodies, funded by an industrial partner, that cross the blood-brain-barrier.

Team 7 (Stéphane Charpier, pages 26-28)

We gratefully acknowledge the positive evaluation and the stimulating recommendations made by the AERES' committee. We would like, however, to clarify some specific issues and inaccurate statements.

The "*causality issue*" is very interesting and should bring into question all experimental research in neuroscience both physiological and pathological. Causality is difficult to demonstrate in fundamental physics and much more so in neurophysiology (for instance the causal relationship between synaptic plasticity and memory formation and recall is not yet established). In our case, we have obtained much experimental evidence that absence seizures are initiated in a restricted region of the cortex, by the initial activation of a specific set of neurons, which are necessary and sufficient for the occurrence of seizures. The use of optogentic tools that target the ictogenic neurons is not sufficient to demonstrate a direct causal link between these neurons and epileptic changes in the whole brain because of the myriad of intermediate neurons and networks that must also be tested. Our current strategy, based on multiple positive correlations, has been fruitful and is further supported by recent findings (unpublished) indicating that "our ictogenic neurons" are the first to exhibit epileptic discharges during post-natal development. However, mathematical causality tools (based on association and directionality between electrophysiological signals) have already been used in our studies, in collaboration with Dr. M. Chavez (CNRS), confirming and extending the experimental findings. They will be further developed by M Le van Quyen (Inserm; already present in the team) and Dr. Mario Chavez, who will soon join our team and will develop new mathematical tools to analyze the spatiotemporal dynamics of our multiscale *in vivo* recordings in normal and epileptic rodents. This crucial recruitment was surprisingly not mentioned in the AERES' report. We are convinced that optogenetic approaches are powerful. They will be developed in appropriate research projects and in collaboration with other teams in the Institute.

The committee mentioned that the "*neurons*" we recorded were not identified. This statement is incorrect. As clearly mentioned in our scientific report (and easily verifiable in our publications), in most of our *in vivo* studies, the neurons were identified by their specific electrophysiological features, morphology and location, *via* intracellular injection of neurobiotin in conjunction with the recordings. Such *in vivo* morpho-functional correlations have always been the starting point of our research. We were thus very surprised by this inaccurate criticism.

The committee recommended that we perform *in vivo* patch-clamp recordings from awake rodents instead of sharp-electrode intracellular recordings in sedated animals, due to strong competition in our fields of research. In fact, in the specific field mentioned, there is no current competition, and we are the only team exploring *in vivo* long-term experience-dependent intrinsic plasticity in the cortex. Moreover, we mentioned in our project that patch-clamp recordings will be made *in vivo* from the rodent cerebral cortex. This technique, acquired by Dr Séverine Mahon during her post-doctoral training in Michael Hausser's lab, will notably allow small neurons, such as interneurons, to be recorded. Our past and future studies (neuronal plasticity and functional impact of spontaneous brain activity) require very long (up to 3h) intracellular recordings *in vivo*, during which the biophysical properties must remain very stable. This challenging experimental strategy, very rarely used in France but employed daily and successfully by our team, cannot be reliably performed with *in vivo*

patch-clamp recordings (see *Hamill OP, McBride DW Jr. Induced membrane hypo/hyper-mechanosensitivity: a limitation of patch-clamp recording. Annu Rev Physiol. 1997*). We will thus use *in vivo* sharp- or patch-clamp recordings, in accordance with the specific scientific and experimental aims of the project. The use of awake animals in this electrophysiological approach (see Mahon et al. 2006) limits the duration of the recordings. They will thus be used only in appropriate projects, *e.g.* when fentanyl sedation (generating wake-like cortical activity, see Bruno and Sakmann, 2006) would interfere with the neurophysiological process studied.
We are grateful for the overall comments and suggestions of the AERES' committee, which were appreciated by the team members and will help us significantly to improve our scientific research and analytic tools.

Team 8 (Bertrand Fontaine and Sophie Nicole, pages 29-31)

We thank the AERES experts for giving us the opportunity to explain more precisely some of the scientific and human aspects of our work. As noted by the experts, the members of the team work smoothly together. This mutual confidence and close collaboration have been important for the human dynamics and the past successes of our team. The recommendations of the AERES experts have, for the most part, already been implemented, thanks to their comments during the site visit. In particular, a bioinformatics platform is being set up through the IHU program in close connection with our team, and an electrophysiology platform is being established under the scientific direction of one of us.
If the Alzheimer program may appear as disconnected by name, P2X7R is a cationic channel receptor involved in cytokines release and is more related to inflammatory response (MS topics) and channel receptors (channelopathy topics) than Abeta production. The sole CRICM team working on AD (Team 3: Alzheimer's and prion diseases) studies the relationships between cholesterol and Abeta, which has no link with P2X7R functions, and thus would not provides appropriate scientific support to the P2X7R project.
The P2X7R and AD project is based on the complementary expertise of the team members. The genetic analysis of P2X7R pathway in AD cases vs controls is rendered possible through the tight interactions within the Fontaine/Nicole team. The researcher in charge of the AD project (Cécile Delarasse) is very well integrated into the team and wants to remain with us to ensure its success. The AD project financially is supported by an ANR-MALZ (Alzheimer's disease) grant (project coordinator: Bertrand Fontaine), which already started in February 2013 for 4 years with the recruitment of a post-doctorant. Finally, we would like to highlight that this project is done in close integration with Team 3 (Alzheimer's and prion diseases, Drs Benoit Delatour and Marie-Claude Potier) as recommended by the AERES committee, and is one example of the close interaction between our team and other teams in the ICM.

Team 9 (Stéphanie Baulac and Eric Leguern, pages 32-34)

"The team has recently identified a gene that harbours frequent private mutations associated with focal epilepsy. This has yet to be published but is a very important finding:"
This study has now been published: Ishida S, Picard F, Rudolf G, Noé E, Achaz G, Thomas

P, Genton P, Mundwiller E, Wolff M, Marescaux C, Miles R, Baulac M, Hirsch E, Leguern E and Baulac S. Mutations of DEPDC5 cause autosomal dominant focal epilepsies. Nature Genetics, Mar 31. doi: 10.1038/ng.2601.

Team 14 (Michel Mallat, pages 46-47)

"Scientific quality and output:" The AERES committee pointed out a lack of major publications since our last paper (J. Neurosci, 2008) on the expression and function of NADPH oxidases (Nox) in microglial cells. Since this publication, our team has made major achievements demonstrating a new physiological function for microglial NADPH oxidases and uncovering a role for microglia in the normal development of astrocytes. Briefly, we have shown that the activity of microglial Nox is required for microglial chemotaxis and infiltration of the cells in the germinative layer of the developing cerebral cortex. Furthermore, we found that these infiltrating microglial cells stimulate cortical astrogliogenesis. These findings were initially presented together in a single manuscript that we submitted, in 2012, to several high IF journals but was not accepted. In order to accelerate publication of at least part of our findings, we have now presented the results in two separate articles. The paper on the role of Nox in microglia cell colonization of the cerebral cortex is presently under review. We are in the process of finishing the second manuscript on the role of microglia in cortical astrogliogenesis.

"Assessment of the five-year strategy / Strength and opportunities / Weaknesses and threats / Recommendations:" In agreement with the committee's remarks, we fully agree that the role of microglia in the developing brain is the most promising aspect of our work, and is consistent with the team's reputation internationally. As pointed out by the committee, this research program generates tools of broad interest, which will be useful for other teams in the institute. The financing of our team is, at least in part, assured up to 2015 because of a recent decision to prolong our INERIS grant. However, the small size of our group raises issues that need to be resolved. As suggested by the committee, we have begun procedures to merge our group with another ICM team "Development, glial pathology and repair." This will generate synergies among scientific expertise, technical skills and human resources, which will benefit our research programs and those of the host team. The discussions are already underway.

Team 15 (Brahim Nait Oumesmar & Anne Baron-Van Evercooren, pages 48-50)

The AERES committee recognized the scientific quality of the team as well as its excellent expertise and international reputation in the field of myelin repair. The five year research plan considered positively.

Regarding the retirement of Anne Baron-Van Evercooren, in February 2016, we would like to insist that the continuity and productivity of the team is ensured. PIs are clearly identified within the team for the different subprojects: 1) Regulation of oligodendrocyte regeneration (PI: B. Nait Oumesmar), 2) PNS stem/progenitor cells and inflammation in CNS repair (PI: V. Zujovic), and 3) Stem cell plasticity with a strong focus on human cells (PI: A. Baron-Van Evercooren). A tenure-track researcher will be recruited to take over Dr. Baron-Van Evercooren's project. A post-doctoral fellow in the

group with strong expertise in human stem cells and iPS will apply for a permanent Inserm or CNRS position in 2014. The team, therefore, has a clear management plan to preserve the continuity and productivity of each of the sub-projects.

Team 23 (Philippe Ravassard, pages 69-71)

First of all, we are pleased that the committee judged our team to be "*unusual.*" Indeed, in parallel with our own research interests, we manage technological platforms and develop services that benefit the whole ICM. Thus, the committee has acknowledged our technological and intellectual contributions to the different scientific programs of the ICM through the development of state-of-the-art technological tools and problem solving.

Concerning our own scientific research, the "Biotechnology & Biotherapy" team has developed interdisciplinary projects for assessing the cross-talk between the brain and the periphery (mind/body) in the development of common neuropsychiatric and metabolic diseases. These projects are rooted in the discovery of a new class of RNAs, the long non-coding RNAs (lncRNAs). Our group discovered the first repertory of lncRNAs in human pancreatic β-cells and understood their relevance, as explained in a seminal article, whereas at least 10 other groups that performed RNAseq in pancreatic β-cells overlooked the evidence in their own data. Although this observation was made in a homogeneous cell population, it paves the way for the discovery of other lncRNA repertories in more complex structures and tissues such as the brain, our next target for the investigation and exploitation of the functional roles of lncRNAs. The identification of the repertories of lncRNAs in different types of neurons and/or brain structures and the study of their functions in the brain will become the main focus of the team. The study of lncRNAs in human pancreatic β-cells, supported by an NIH grant (the lncBeta program), allowed us to acquire the know-how for mapping lncRNAs and for studying their function. This will be used to discover new repertories of lncRNAs in brain-specific cell types in normal and pathological situations. More specifically, we have already identified lncRNAs specific to dopaminergic and/or serotoninergic neurons in mice, paving the way for analogous studies in human neurons. Human dopaminergic and serotoninergic neurons will be derived from IPS cells. We have already established a close collaboration with a leading group in the field of iPS cells (Austin Smith) and will take advantage of the newly created iPS cell platform at the ICM. Our team will be reorganized to focus on the study of the role lncRNAs in human neuronal populations in normal and pathological situations, in complete accord with the scientific objectives of the ICM.