IFM - Institut du fer à moulin

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Institut du Fer à Moulin

IFM UMR-S 839

Under the supervision of the following institutions and research bodies:

Université Paris 6 - Pierre et Marie Curie

Institut National de la Santé Et de la Recherche Médicale

February 2013

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

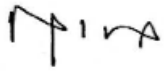
Research Units Department

President of AERES

Didier Houssin

Research Units Department

Department Head



Pierre Glaudes

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

Grading

Once the visits for the 2012-2013 evaluation campaign had been completed, the chairpersons of the expert committees, who met per disciplinary group, proceeded to attribute a score to the research units in their group (and, when necessary, for these units' in-house teams).
This score (A+, A, B, C) concerned each of the six criteria defined by the AERES.
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, when necessary, its in-house teams) received the following grades:

- Grading table of the unit: Institut du Fer à Moulin

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

- Grading table of the team: Neurotransmission and signaling

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

- Grading table of the team: Cortical development and pathology

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

- Grading table of the team: Plasticity in cortical networks and epilepsy

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

- Grading table of the team: Neurotransmission in neural circuit development

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

- Grading table of the team: Serotonin signaling in plasticity and disease

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

- Grading table of the team: Neurodevelopmental disorders

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

- Grading table of the team: Synapses and pathophysiology of reward

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

Evaluation report

Unit name:	Intitut de Fer à Moulin
Unit acronym:	IFM UMRS 839
Label requested:	
Present no.:	
Name of Director (2012-2013):	Mr Jean-Antoine GIRAULT
Name of Project Leader (2014-2018):	Mr Jean-Antoine GIRAULT

Expert committee members

Chair:

Mr Abdelhamid BENAZZOUZ, Université Bordeaux Segalen, Bordeaux

Experts:

Mr Mohamed JABER, Université de Poitiers, (Representative of INSERM CSS)

Mr Karri LAMSA, University of Oxford, United Kingdom

Mr Beat LUTZ, Johannes Gutenberg University, Mainz, Germany

Mr Guy MENSAH-NYAGAN, Université de Strasbourg, (Representative of CNU)

Mr Laurent NGUYEN, University of Liège, Belgium

Mr Trevor SHARP, University of Oxford, United Kingdom

Mr Pierre SZEPETOWSKI, Institut de Neurobiologie de la Méditerranée, Marseille

Scientific delegate representing the AERES:

Mr Patrick BLADER

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

Mr Etienne HIRSCH, INSERM

Mr Paul INDELICATO, vice-Président Recherche/Innovation, UPMC

1 • Introduction

History and geographical location of the unit

The "Institut du Fer à Moulin" (IFM) was created in 2007 after the fusion of three INSERM Units: U.536 headed by Jean-Antoine Girault, U.706 headed by André Sobel and U.616 headed by Patricia Gaspar. The IFM then welcomed a Clinical Neurologist, Jacques Hugon, who headed the "Centre mémoire de ressources et de recherche" and Fiona Francis, who obtained an INSERM Avenir grant. In 2008, the IFM was evaluated by the AERES, whose conclusions were very positive. Later, the IFM recruited two new young researchers (Matthias Groszer in 2009 and Manuel Mameli in 2010), who each obtained a highly competitive Avenir grants and permanent CR1 INSERM positions. In total, over the current review period the IFM comprised 6 senior teams (Girault/Hervé, Poncer/Levi, Gaspar, Maroteaux, Sobel and Mège/Métin), three junior groups (Francis, Groszer and Mameli), and a translational platform (Vigny and Hugon).

The IFM is affiliated with INSERM and "Université Pierre et Marie Curie" (UPMC). It is housed in an INSERM building in the neighborhood of UPMC and "Hôpital la Salpétrière".

The research objective of the IFM focuses on understanding the development and plasticity of the nervous system, which is organized along two major research axes: 1) cortical development and its alterations responsible for neurodevelopmental disorders leading to intellectual disability, autism and epilepsy; 2) plasticity in the adult nervous system, its pathology and pharmacological control.

Management team:

The IFM is headed by a director, Professor Jean-Antoine Girault, and two vice directors, Drs André Sobel and Patricia Gaspar.

A Research Center Council (Conseil du Centre de Rechercher, CCR) composed of the team leaders and representatives of the personnel makes decisions regarding the organizational and practical issues. Important decisions are submitted to a vote by the CCR.

The research teams are scientifically independent and the leader of each team is responsible for his scientific projects, strategy and funding.

AERES nomenclature:

SVE1 LS5

Unit workforce:

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	7	6	6
N2: Permanent researchers from Institutions and similar positions	20	19	19
N3: Other permanent staff (without research duties)	20	15	3
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	0	0	0
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	17	17	15
N6: Other contractual staff (without research duties)	6	5	0
TOTAL N1 to N6	70	62	43

Percentage of producers (calculated as total column 2 / total n of people column 1, but only those who were present at 01/06/12)	***90.01 % (40/44)***

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	13	
Theses defended	22	
Postdoctoral students having spent at least 12 months in the unit*	15	
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	13	12

2 • Assessment of the unit

Strengths and opportunities:

The IFM was created as a Neuroscience Center five years ago and in this short period of time it has become an internationally acknowledged Institute. The core scientific teams were selected from existing research groups of the merged Inserm units. In addition 3 new teams were established by recruiting young scientists who subsequently obtained ATIP/Avenir funding.

The intellectual and scientific environment at the IFM is very attractive for scientists, thus, promoting the success of the projects.

The IFM members have expertise in a selection of research disciplines including, genetics, molecular biology, cellular biology, biochemistry, neuroanatomy and electrophysiology.

The IFM is organized in such way that shared scientific equipment are based in common facilities and rooms accessible to all the teams. These include their two major core facilities "plateformes": 1) state-of-the art functional cell and tissue imaging system, including 2-photon and electron microscopes; 2) mouse breeding and experimentation space, including a L2/A2 viral vector transfection room, surgery room and separate rooms for behavioral tests. This animal facility will undergo major renovation in 2013. A new facility is planned to be developed with culture facilities for neuronal differentiation of induced pluripotent stem cells harvested from genetically altered mice and human patients. This will strengthen the investigations of pathophysiological mechanisms of neuropsychiatric disorders with a strong genetic component.

Several IFM researchers have been involved in improving methodological and technological approaches and many have contributed to the development/implementation of powerful technologies beneficial for the whole institute.

There are many ongoing interactions/collaborations between the IFM research groups that positively impact on the scientific quality and productivity of the institute. Such collaborations have generated 11 co-authored publications since 2008.

Weaknesses and threats:

The projects rely on a functional mouse facility. However, this facility will be renovated in the coming year. During this 'down-time', the function of the animal facility will inevitably be compromised. It will be critically important to organize adequate space and sufficient capacity for breeding and maintenance of animals, as well as for performing behavioral experiments. As the renovation start date is still not clearly defined, due to the renewal of an administrative permit, there is an uneasy ambiance amongst the animal facility personnel. This is likely to feed back onto the progress of ongoing research work.

Several proposed projects are reliant on behavioural experimental approaches, which require personnel with training and expertise in behavioural neuroscience. There is a need of such experts in the IFM. One senior scientist-level expert in mouse behavioural studies has already been recruited at the IFM, but given the size of the institute and volume of research proposed, additional recruitment is needed. Otherwise, failure to establish some of the proposed projects is possible.

Small size of some teams makes the feasibility of the projects vulnerable.

Translational aspects of many of the projects are still at an exploratory stage.

Recommendations:

It is critically important to resolve the current situation regarding animal maintenance and breeding, otherwise, many of the projects will be seriously challenged.

It is recommended that the IFM leaders define a clear strategy to solve questions related to the critical mass of several teams.

It is recommended that some teams streamline their research plans and focus on projects with highest interest and feasibility.

The Committee recommends that the IFM improves translational aspects of its research by building collaborations with neurologists and psychiatrists. An excellent opportunity for such developments is offered by the Labex Bio-Psy initiative, for which the institute's director is the coordinator and scientific director.

The Committee considers it important that the Unit formulates a strategy to recruit experts in behavioral neuroscience to improve synergies of the existing expertise.

3 • Detailed assessments

Assessment of scientific quality and outputs

Given the medium size of the institute and the fact that it is too early for some young teams to fully demonstrate their contributions, the scientific output is of excellent quality. The Unit has published more than 163 papers in peer-reviewed journals since 2008. Among the most important papers that were led by researchers from the Unit (as first, last and/or corresponding author) are: Nature, Science, PNAS (2), Mol Psychiat. , Nat Neurosci. (2),Neuron, J Cell Biol., Blood, Brain, Neuropsychopharmacology (3), J. Neurosci. (14), J. Cell Sci. , Hum Mol Genet., ereb Cortex.

The committee noted that the productivity of individual teams is not uniform. A small number of teams have tended either to publish only in specialised journals or principally in collaboration with large research consortia.

In addition to the overall excellent quality and volume of original publications, the IFM members obtained two patents: one for a biomarker in Alzheimer's disease (2011) and one for new dual biomarkers of neurodegeneration and neuroregeneration (2012). Licensing of these two patents is under negotiation.

Assessment of the unit's academic reputation and appeal

IFM scientists are involved in a large network of collaborations, in the Paris area as well as nationally and internationally, including Europe, America, and Japan.

The visibility of the IFM has benefited from the organization of the « Ecole des Neurosciences de Paris-Ile-de-France » (ENP), a regional network of excellence with a commitment to facilitate interaction between high quality labs in the Paris region and attract the best international students. The ENP project was coordinated by Prof. J.A. Girault who was its first director until 2010. It is now headed by Dr Patricia Gaspar.

The IFM research teams participate in a Laboratory of Excellence (Labex) project, entitled Biological Psychiatry (Bio-Psy). This Labex is coordinated by Prof. J.A. Girault, with Dr P. Gaspar as vice-director responsible for training and education.

The high quality of group leaders at the IFM is attested to by the numerous grants and awards they have received during the past five years. These include 3 Avenir grants, 2 NARSAD, 2 Ville de Paris young investigator awards, 1 ERC advanced grant, 3 "FRM team" awards, 1 "Coup d'élan Bettancourt" award, and 1 Janine Courtier prize from the National Academy of Sciences. In addition, a number of competitive fellowships for post-docs or research training of medical fellows/visitors have been obtained.

IFM scientists are frequently invited to give lectures at national and international institutes and conferences, and they have also been involved in the organization of various national and international meetings.

The IFM has been extremely successful in attracting PhD students and post-docs, who represent about 50% of the total members of the institute. The proportion of international young scientists from the undergraduate to the post-doc level is increasing, attesting to the international visibility of the IFM.

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

IFM scientists have contributed to the "Week of the brain" and other public awareness campaigns. They have also participated in radio and TV programs presenting topics on brain diseases, and they have given lectures to the general public. An IFM member was recently elected as a member of European Dana Alliance for the Brain (EDAB), which aims at making neuroscience more familiar and better known to the public.

The IFM has hosted visits and presentations for distinguished guests in collaboration with Inserm (e.g., China ambassador, Kenya representative, members of Scientific office of the French parliament, minister of Research, Cour des Comptes…) or with FRM (site-visits for donators). Several site visits and short internships for high school students were organized, and several IFM scientists participated in training programs for high school students.

Assessment of the unit's organisation and life:

The IFM's scientific activity is organized along two main axes: brain development and plasticity. These axes offer opportunities for multiple collaborative interactions amongst the group leaders. For example, several teams study cortical development and how its alteration in neurodevelopmental disorders leads to intellectual disability, autism spectrum disorders (ASD), and epilepsy. In addition there are interactive projects combining neuronal plasticity in the adult nervous system and associated pathologies.

The IFM is organized in such a way that shared scientific equipment is located in common facilities accessible to all teams. An important effort has been made to increase the availability of shared equipment by using common resources and by submitting joint applications involving several IFM teams.

The equipment sharing and a common social room facilitates informal day-to-day exchanges between personnel including students and post-docs. There are many ongoing interactions between the IFM research teams generating collaborations, which are strong and productive.

Each week the IFM organizes two meetings attended by all IFM scientific members. One meeting is on Mondays where two scientists or students present their ongoing work. The other meeting is centred around a seminar series involving invited guest lecturers. Recently PIs have started a regular "Chalk talks" meeting during which they briefly present their ongoing projects to their peers in the IFM.

Overall there is a strong impression that members of the IFM are very happy in the unit, and that they appreciate its hard-working habits and pleasant atmosphere. However, there is a justified ongoing concern regarding the animal facilities, which is making people feel quite uncomfortable. However, there appears to be a generally optimistic outlook, and assumption that the problem will be solved very soon.

There may be a need to have a more direct and organized information flow on future plans and on the overall strategy inside the unit. Selected representatives regularly participate in management meetings and transfer the information to their colleagues whenever needed, and this seems to work well. However, this may not be sufficient in all instances, since news does not necessarily reach every member in the team (as an example personnel working in the animal facility).

The committee sensed that members of the permanent staff would benefit from having more formal discussions and information on their own careers. The MCU/PU staff (lecturers) would also benefit from being supported during the periods of intensive teaching (e.g. technical support for experiments).

Assessment of the unit's involvement in training through research

The IFM senior scientists are highly involved in teaching and training activities. The University lecturers have strong teaching commitments, and several researchers are also involved in teaching courses or lectures at UPMC, Paris-Descartes University, the Ecole Normale Superieure and the ecole Polytechniques. Several courses and practicals are organized at the IFM, thereby increasing the visibility for students and medical interns. The IFM participates in the training of undergraduate students, including Master students, M1 and M2 degrees. A large number of PhD students obtained their diplomas (27) in the period of time between 2007 and 2012. The leader of Team 4 is the present director of the Paris Neuroscience School (ENP).

Assessment of the five-year plan and strategy

The candidate Director is Professor Jean-Antoine Girault and the candidate Vice-Director is Dr Fiona Francis. Seven teams are proposed for the next 5 years, with no major organizational change because the IFM has reached a state of efficient organization.

The general scientific aim of the IFM is to better understand the molecular and cellular mechanisms that underlie brain development and plasticity, with various complementary aspects using different techniques and approaches and many points of convergence on topics important for biomedical research. The committee considered that the proposed projects are of excellent quality, and led by scientists with solid reputations and good visibility in their respective fields.

Although IFM researchers are largely involved in basic research, all teams have a strong interest for medical issues and applications. Their involvement in the Bio-Psy Labex offers the unique possibility to strengthen the basic neurobiological research through interactions with researchers focused on the clinical aspects of neurological and psychiatric diseases. This is an excellent opportunity which will allow the IFM teams to reinforce their national and international position and visibility.

In the next research programme, IFM teams aim to strengthen their expertise in molecular and cellular approaches to neuroscience, in close association with other approaches. This will be achieved by the reinforcement of existing teams and common facilities, as well as by welcoming one or two new groups during the next 5 years.

4 • Team-by-team analysis

Team 1 : Neurotransmission and signaling

Name of team leader: Mr Jean-Antoine GIRAULT and Mr Denis HERVÉ

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	1	1
N2: Permanent EPST or EPIC researchers and similar positions	3	3	3
N3: Other permanent staff (without research duties)	1,5	0	0
N4: Other professors (PREM, ECC, etc.)	0	0	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	4	5	4
N6: Other contractual staff (without research duties)	1	1	0
TOTAL N1 to N6	11,5	10	8

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	3	
Theses defended	9	
Postdoctoral students having spent at least 12 months in the unit	6	
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

During the evaluation period 2008-2012, Team 1 has produced 36 original research articles, 13 reviews and 1 book chapter. The impact factors (IF) of the published papers were generally very high, starting with IF 3.5/4 at the lowest, but most journals are in the range of IF 6 to 10, some between IF 15 and 20, and two at IF 30-32 (Nature, Nature Genetics). This is exellent quality. In addition, papers published by Team 1 have been highly cited in the literature. H-factors of the two team leaders are 54 and 40. It is important to note that many of the high-impact publications by Team 1 has the team member as the first and/or last author (e.g., the Nature paper in 2008). The Book Chapter in Neurobiology of Mental Illness (edited by D. Charney and E. Nestler) reflects the international standing of Team 1. Considering the relatively small number of group members in Team 1, the quality and quantity of publications is excellent. This indicates thoughtful and innovative design of projects, successful data acquistion and efficient writing of publications.

Assessment of the team's academic reputation and appeal

Team 1 has an excellent representation of international students. Overall 21 students (undergraduate or graduate students, post-docs) from Europe, Asia and America have joined the lab during the evaluation period. The group leaders have given more than 34 invited lectures abroad. In addition Team 1 participates in a Marie Curie Initial Training Network (NPlast), and one of the team leaders recently acquired a highly prestigious Advanced ERC Grant. Furthermore, Team 1 actively maintains several international collaborations very successfully (as also apparent in the list of publications). The more senior team leader is currently in the Editorial Board of Faculty of 1000 and of Addiction Biology. He is also present in several national and international Scientific Boards and Study Sections. Based on his excellent reputation and scientific recognition, he was appointed as a coordinator and first Director of the Paris School of Neuroscience (2007-2010). Members of Team 1 are strongly involved in the organization of various scientific meetings both nationally and abroad (one in Switzerland). In summary, Team 1 has an excellent national and international visibility, and as a testament to this it has attracted students and post-docs from France (Paris and other areas), Europe and Overseas.

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

Team 1 has two contracts with industrial partners. The research themes of addictions and neuronal signalling in the striatum are of high public interest. One of the team leaders has participated in two radio broadcasts on topics of drug addiction and neurodegenerative disease (Parkinson's Disease). They have given public lectures, and written 2 papers in Médicine/Science, a scientific journal that popularizes sciences for the general public.

Assesment of the team's organisation and life:

Team 1 is well integrated into the IFM; there are three active collaborations between Team 1 and other teams of the institute. Team 1 has a very good group structure with a balanced between master students, visiting scientists/students, Ph.D. students, and post-docs. It is clear that Team 1 is very well organized. The supervisors are able to share duties and responsibilities when one of them is absent, due to other scientific obligations.

Assessment of the team's involvement in training through research

There appears to be a very stimulating atmosphere for education and training of students. Many international students have joined the group. The Ph.D. students have successfully defended their thesis, and, most importantly, many Ph.D. students continued their research via post-doctoral training abroad. One of the group leaders is involved in a FP7 Marie Curie Initial Training Network and is centrally involved in the Paris School of Neuroscience. The two group leaders and several scientists of Team 1 gave lectures and practical courses at UPMC. During the evaluation period 7 master students educated from the group.

Assessment of the five-year plan and strategy

The research plan is very much in line with the earlier work of Team 1. It consequently follows up previous interesting observations, now implementing numerous innovative methodological approaches (e.g., FRET, FRAP, time-lapse live imaging, 2-photon microscopy with electrophysiological recording, optogenetics, RNA sequencing, epigenetic analysis of specific neuronal subpopulations isolated by FACS, genetic marking of activated neurons in vivo in transgenic mice). Although the program undoubtedly is busy and challenging, and contains some risky subprojects, experimental approaches are carefully and thoughfully designed. Hence, exciting results can be expected, and it is anticipated that some of the discoveries will lead to high profile publications. This research program aims at elucidating the neurobiology of striatal functions in the context of incentive learning and inhibitory learning. This theme is central to the understanding of addiction and it is possible that novel approaches will emerge from this research that will allow to treat disorders with disturbed incentive learning.

Conclusion:

- Strengths and opportunities:

The research theme is very relevant to medical sciences and neuropsychiatric disorders. Team 1 has an excellent record in this field of research, and it is very likely that the projects will be mastered from the technical point of view. The environment at the IFM and the group structure is very attractive for scientists, thus, promoting the success of the projects.

- Weaknesses and threats:

Some aspects of the team's project are risky and it will be important to manage/distribute this risk, in order to avoid failures of individual (student / post doc) careers. Although high turn-over of scientists is a strength and power of the group, it may also have some downsides. Furthermore, the projects rely on a functional animal facility which will shortly be renovated. During the time the animal facilities are compromised, it will be critically important to organize room for breeding, maintenance and performance of behavioral experiments.

- Recommendations:

During the next evaluation period the committee considered it critically important to ensure animal maintenance and breeding capacity, and facilities for behavioral experiments and analysis. Without this, many of the projects may be seriously challenged. Furthermore, the group leaders might have to focus on subprojects with highest feasibility. It will be equally important to support continuity within the group in addition to the large number of visitors and high turn-over of scientists during time.

4 • Team-by-team analysis

Team 2 : Cortical development and pathology

Name of team leader: Ms Fiona FRANCIS and Ms Laurence GOUTEBROZE

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	1
N2: Permanent EPST or EPIC researchers and similar positions	2	4	2
N3: Other permanent staff (without research duties)	0	1,5	1
N4: Other professors (PREM, ECC, etc.)	0	0	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	0	1
N6: Other contractual staff (without research duties)	1	0	0
TOTAL N1 to N6	5	7,5	5

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	0	
Qualified research supervisors (with an HDR) or similar positions	1	2

• Detailed assessments

Assessment of scientific quality and outputs

The team investigates the role of cell cytoskeleton-related genes that contribute to cerebral corticogenesis and whose misexpression is associated with subcortical heterotopia (SH) in human and mouse. For this, the team uses state-of-the-art technologies that include mouse genetic, cell biology, time lapse recording, histology and biochemistry. The team is also actively collaborating with national and international scientists that have complementary expertise.

In the past, the team concentrated on the cortical phenotype of TUBA1 mutations (associated with human lissencephaly) and they are now currently adressing the effect of such mutations on neuronal migration in the cortex and the rostral migratory stream in the adult brain. In the framework of an ANR project, the team characterized the anatomy, physiology and epileptiform activity of the hippocampal CA3 region of the adult Dcx knockout mouse as well as their impact on behavior and memory. The main achievement of the team is the identification of a novel heterotopia gene (EML1) in both human and mouse. This gene is little-studied and has never been associated with SH. They are currently analysing its function in cortical cells from mouse and ferret in a collaboration with experts outside the IFM. Since the creation of the IFM this team has published in several very good quality journals, including a very significant paper in Brain (IF=9.5); the unpublished data supporting novel functions for EML1 in corticogenesis are likely to be published soon in a top level scientific journal and open doors for further exciting discoveries. One team leader has been invited to international meetings to present the data of her team. Thus, the team is overall building up an international reputation and shows a net progression of scientific quality.

The present team is the merger of two teams, and the arrival of a permanent researcher will create synergies between scientists that show convergent interest and complementary expertise. One of the founding groups has been studying the molecular and cellular regulation of axoglial contacts in myelinated fibres with a particular emphasis on the CNTNAP2 gene that code for Caspr2 protein. Mutations in the CNTNAP2 gene have also been recently associated with psychiatric and neurological disorders. In the future, a new CNTNAP2 project on cerebral cortical neurogenesis more in phase with the existing research of the second founding team is proposed that aims at identifying neurodevelopmental roles of Caspr2 in health and disease by combining models including transgenic mice and human induced pluripotent stem cells from patients (iPSc).

Overall, the project of team 2 is competitive as it includes the analysis of proteins (Eml1 and Caspr2) whose roles in cerebral corticogenesis (in health and disease) remain poorly characterized. In addition, the Dcx-based project balances nicely the high risk/high gain aspects of the other parts of the team project.

Assessment of the team's academic reputation and appeal

One of the future team leaders was awarded with the "Coup d'Elan Fondation Bettencourt Schueller Prize (2008). This team leader also received five years support from an "AVENIR" grant (2009) and coordinated large scale scientific projects, including one ANR (2009) project and one FRC project (2011), and also recently started a Hubert Curien al Maqdisi project. The second group leader coordinated an ANR project.

Both PIs have established a national and international network of collaborations and have published in top neuroscience journals, including Brain and Journal of Neurosciences, which brought them international recognition in their respective fields. In addition, they have been invited abroad to present their work. Both PIs are are regularly contributing to PhD jury (both PIs) or HDR defenses, they are members of several scientific societies and they act as reviewers for renowned scientific journals, including J. Neurosci., Hum. Mol. Genet.,..

Overall, the team has a good national and international visibility.

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

One of the PIs has exposed the reviewing process for FRC grants to the general public (newsletter "Synapse") and has described group activities for the general public (Annual newsletter "Recherche en Tête). In addition, this PI regularly communicates the last research progresses to family of patients suffering from lissencephaly. The result of the team's research will likely provide insights into some inheritable cerebral cortical diseases and thus boost translational research. The team has also collaborated with the industry that has led to a joint submitted manuscript.

Assessment of the team's organisation and life:

Team 2 results from the fusion of two groups. This novel team is dynamic and well integrated into the IFM; Team 2 has several ongoing collaborations with other IFM teams (1, 6…). Team 2 has a solid and well organised structure with balance between master students, Ph.D. students, and post-docs. Both team leaders have international reputations in their respective research fields and are complementary in knowledge and know-how. They will share duties and responsibilities in the group.

Assessment of the team's involvement in training through research

Both PIs have experience in supervising scientists (technician, PhD students and postdocs). The first attracted five foreign students, which emphazises the notoriety of the team. In addition, teaching of master courses and other periodic teaching activities which helps attracting new students to the lab. The second PI is responsible for organizing the internal PhD committee. There are two additional lecturers in the team and the lab belong to the ENP that should help renewing the undergraduate student pool in the future.

Assessment of the five-year plan and strategy

The new group will include scientists with complementary competences (one is neurogeneticist with biochemistry experience and the other is molecular biologist with geneticist expertise) and experiences necessary for the projet. Within the IFM, the group will have access to basic equipment required for biochemistry, molecular biology, cell biology, histology, immunohistochemitry, time lapse imaging.

The project is of good quality overall and composed of three integrated axes. Most parts of the projects are supported by preliminary data and balance high-risk/high-gain aspects with less competitive but safer ones. Although, the second team leader has so far mostly been working on the molecular regulation of axon myelination, she has a great knowledge of Caspr2 biology and masters tools required to develop a novel project on corticogenesis. Her integration into the future team will help acquiring knowledge and tools required for analysis of cerebral cortical development. Although aims of each axis are clearly defined, the experimental procedure would need to be clarified and the rationale of some experiments lacks in project 2. The project does not include options that would be taken if some experiments would not work.

Conclusion:

- Strengths and opportunities:

Merging two teams will likely create synergistic interactions that will impact positively on the quality of their respective scientific production and increase their international visibility. The future group is large and stable, and is also dedicated to training of PhD students who can be attracted by the lecturers of the group.

The project is competitive and balances high-risk/high-gain axes with a safer one. The project involves basic research but opens doors to translational research as it relates to highly relevant medical issues.

- Weaknesses and threats:

Help with bioinformatic analyses may be needed to permit exploitation of data in timely manner.

It would have helped to have information on the options that would be taken if some experiments/main teams are not as successful as expected. Some parts of the project are risky because of high competition elsewhere (another group is working on the CASPR2). Experiments performed with human iPS cells are tricky and time-consuming. Unfortunately the feasibility of this part of the project is difficult to assess as the team has no previous experience with such cells. They may benefit from establishing a collaboration with a group with expertise in this area.

● Recommendations:

This is an excellent project with scientists who have solid reputation in their respective fields.

Project 1 on Eml1 : Tracking EB3-GFP comet like streaks will only give an estimation of MT polymerisation. The analysis of other MT dynamic parameters (depolymerisation, …) required the direct monitoring of tubulin (e.g. analysing MT-incorporated alpha-tubulin-GFP).

Project 2 : The committee suggests putting significant effort toward the exact experiments planned with hiPS cells as 1/hiPS handling is tricky and time-consuming; and 2/the lab does not seem to currently master such technology.

4 • Team-by-team analysis

Team 3 : Plasticity in cortical networks and epilepsy

Name of team leader: Mr Jean-Christophe PONCER and Ms Sabine LÉVI

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

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	2	
Theses defended	2	
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	2	2

• Detailed assessments

Assessment of scientific quality and outputs

Given the relatively small size of the group and the fact that it is clearly in its early phase of development, the productivity of team 3 is of excellent quality and volume. The group has independently published one study in PNAS (outstanding, a general science journal) and two papers in the Journal of Neuroscience (excellent, a leading special topic journal) and one paper in the Cerebral Cortex (excellent, a top special topic journal). These original research publications establish the backbone of the team's future research agenda. Naturally, one of the two team leaders has made a larger contribution as a more senior PI than the other who is just applying for independent principal investigator status as co-head of the team. The more senior group leader has published four last author research papers (including the above mentioned paper in PNAS and two in the Journal of Neuroscience). The younger group leader has proven potential to lead a research group by having two independent corresponding author papers published recently, one of which is the above mentioned in Cerebral Cortex.

Both PIs have contributed to seven review articles in visible and respected peer-reviewed journals, and in five of them they have either been first or a corresponding author. This is a considerable number of reviews in a five-year period, and also a good testament to the standing of the PIs within their field.

Assessment of the team's academic reputation and appeal

Despite its relatively small size and early stage of independence, this is a very dynamic and a highly productive group. The more senior co-head of the team is internationally recognized and has high-quality and original publications on timely topics in mainstream journals. The junior co-head has recently had two last-author publications in peer-reviewed journals one of those in Cerebral Cortex, which is a visible publication forum in the neuroscience field. Recent main publications of the team are characterized by originality and fresh intellectual angles. This applies to the publications underlying both of their two major research topics.

The more senior team leader was awarded by highly competitive support via the Avenir program in 2006. During 2007-2012, the group has been very successful in gaining additional research funding including active research grants from ANR and Ville de Paris. These are very good indicators of an excellent reputation and recognition within the scientific community.

In addition both PIs have been invited to present talks at several national and international symposia and conferences. This shows very good international visibility of the team's research results.

The senior team leader has participated in the organization of national (2x) and international meetings.

Both team leaders have attained academic visibility at an early stage of their careers. The more senior team leader is a review editor for the Frontiers in Synaptic Neuroscience. Both PIs are regular reviewers for scientific journals.

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

The group has ongoing collaborations with industry in France concerning fiber-optic based system for photo-uncaging and testing optically-sensitive ion channels (opsins). The team has participated meetings and seminar organized by industry (Scientifica). The group is an active partner in national and European Ph.D. student training networks (e.g. Erasmus-program).

Assesment of the team's organisation and life:

The group was established in 2006 and in 2007 it joined the IFM whereupon it has gradually grown to its current form. In addition to the senior team leader, the other two key persons in the team have been trained in the group during 2007 and 2012. In the future, the group will be co-directed by two PIs, whilst the other "junior" team member will remain, thus preserving critical expertise and skills in the team. This person is currently in the team as a postdoctoral fellow, whose funding was organized by the group. The group is actively applying for further funding for this person, who will also be applying for the permanent position, which will be allocated to this group in September 2013.

The group is well structured around two PIs with profiles that complement each other. The committee appreciated that the team leaders co-operation works extremely well, and that their fusion into one group is a natural move to make. It is worth mentioning that the team leaders have known each other more than fifteen years, and successfully worked together in the past. Securing a position for the key postdoc in the group will be critical for everyday supervision of students and visitors, and for uninterrupted scientific productivity of this team. The group has sufficient expertise, and importantly, independence required for experiments presented in the research plan. In addition the group has excellent collaborators who are all dynamic young leaders in their field.

The group is also closely and efficiently interacting with another young and productive team at the institute working on synapses and pathophysiology of reward (team 7).

It is realistic that the team will resolve many of the research questions defined in their 5 year plan. The applied funding mentioned in the plan can have strategic importance for development of the group. It is currently at a stage where it could, with good support, become a truly international leader in their field.

Assessment of the team's involvement in training through research

The team has trained/is training four PhD students and has altogether trained nine Masters' or equal level students in the lab. This is a high number for a relatively small group and clearly indicates the commitment of the group to the training of academic students and is also a testament to the group's visibility and good reputation. It is noteworthy that the first PhD students have produced (or will soon produce) first author research articles from their work in the team. In addition, an MSc student is a first author in a publication in Cerebral Cortex.

Key members of the team play an active role in national Master's training program. The senior team leader is a co-ordinator and both team leaders are teachers in Master's courses. In addition the senior team leader is actively involved as a co-ordinator and advisor in the network of European PhD school of Neuroscience. He is also a council member in the major PhD training program in the Paris area.

The more senior team leader organizes weekly seminars for PhD students to present their data and on-going projects in the institute. He is also a member of board in a PhD and an MCU committee.

Assessment of the five-year plan and strategy

Structure and quality of the suggested 5-year plan: The group's five-year plan focuses on their two recent major discoveries. The first is on the K-Cl transporter molecule's surprising role in regulation of glutamatergic neurons' microscale structure and glutamatergic synapse strength and dynamics. The other part of the plan will concentrate on alterations in specific inhibitory neuronal circuits driven by paroxysmal neuronal activity during development of epilepsy. In general this is a well-structured high quality plan, which relies on the research group's own major original discoveries and is designed in a way that it has relevant back-ups in case the suggested main hypotheses fail.

Originality, schedule and probability to be finished in suggested time line: Although both major research topic fields are competitive, and there undoubtedly are rival groups, the team has original and fresh angles to the research topics. The original findings of the group will give them a head start against the competition and provide an original niche in the field. Their novel discovery on K-Cl transporter's interaction with glutamatergic synapses is surprising and exciting. The team's established position in this field and the amount of unpublished results should give them an advantage to publish their future projects without an immediate threat to become severely scooped.

The team's novel results on long-term synaptic plasticity in parvalbumin-expressing inhibitory cortical interneurons are equally timely and important, although there are other research groups working on this phenomenon in the field. However, as the team mentions in the research plan, they are focusing on a less competitive niche in the field and concentrate on one important inhibitory circuit type and its plasticity in specific pathological stages.

Request for additional instruments mentioned in the 5-year plan would be justified concerning natural growth of the group size.

Aspects that may require special attention: A major threat would be that one of the key personnel leave or is forced to leave during the projects as this would disable the group's solid structure and substantially compromise its productivity. Smooth operation of the group during the 5-year period will be important, because both of the suggested research topics are in competitive fields. The team has planned very wisely and is recruiting skilled postdocs and students to provide a good structure to the group with experienced middlemen in specific research techniques. The team has good plans to secure salary and a permanent position (one assistant professor position at the UPMC for September 2013) for the key members of the lab and this is very important. A skilled postdoc trained in the laboratory and a technical expert (engineer or technician) would ensure uninterrupted proceeding of the research plan.

Conclusion:

- Strengths and opportunities:

This is an original research plan aiming to study two well-defined, timely and important research questions. The five-year research plan is well designed, concise and relies on realistic goals. The group's growing plan will reinforce the team with new recruits and secure position of their key post doc in the group. These are both important for a growing multidisciplinary group if it wishes to keep technical expertise in the team and stay independent. Both of the research projects have potential translational aspects. Yet inhibitory cell plasticity in epilepsy is more likely to result in clinically interesting experiments first. The plan to continue the work on epilepsy in vivo with a collaboration group has substantial potential for clinical interests. Future plans for possible research results are carefully considered. The team has relevant back-ups in their projects in case hypotheses fail.

In general this plan has a good cost benefit ratio. The team is experienced, independent and it has chosen excellent and dynamic research collaborators. It is highly likely that the plan suggested here will produce important discoveries with high significance in the field with in the 5 years' time line. It is likely that some of these results will be published in very prestigious high impact journals during the next evaluation period.

- Weaknesses and threats:

The team operates in a competitive research field. Both the KCC regulation and plasticity of inhibition are busy areas. Several strong research groups work on these topics. Yet, the team has an original angle in both research areas, which is importantly based on their own published discoveries.

The proposed work involves multiple techniques, which are either rather complicated and require trained personnel or are novel non-standard techniques which may not work as expected. Yet, these are unavoidable situations in innovative research. Unexpected delays or even failures to establish some of the suggested applications are possible.

Small size of the team makes it vulnerable. To secure the team's research work and its productivity, it is strategically critical to secure key members position within the team. This involves stable funding for at least the senior trained postdoctoral fellow.

Translational aspects of the projects are still at a speculative stage.

- Recommendations:

Secured funding of key players of this team will be critical for seamless working of this multidisciplinary team with high expertise and skills. Success with the following 5 year research plan will be important for this team's future role in the field. The team is already internationally recognized from its original scientific discoveries and it has realistic changes to become a true world leader in the field.

4 • Team-by-team analysis

Team 4 : Neurotransmission in neural circuit development

Name of team leader: Ms Patricia GASPAR

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	1
N2: Permanent EPST or EPIC researchers and similar positions	2	3	3
N3: Other permanent staff (without research duties)	2	1	1
N4: Other professors (PREM, ECC, etc.)	0	0	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	3	2
N6: Other contractual staff (without research duties)	1	0	0
TOTAL N1 to N6	8	8	7

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	3	
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 team joined the IFM in 2007 with a project focused on understanding the mechanisms of neural circuit development. More specifically, the group works on the role of serotonin in developmental plasticity. Undoubtedly, the very good scientific quality of the team constitutes an added value for IFM. Indeed, the elapsed 5 year period of time was marked by several papers (17) published by the team in peer-reviewed journals including highly profiled neuroscience journals including Journal of Neuroscience (x 4). Also, the team members provide strong and useful expertise in histology and anatomy for other IFM-groups. In addition, the team members are involved in several national and international long-lasting collaborations. Noteworthy is the fact that the team leader has coordinated a European multipartner grant and 2 ANR projects. Therefore, the team has a commendable publication record and a very good international visibility.

Assessment of the team's academic reputation and appeal

The team leader is a board member of 3 neuroscience journals (J. Neurosci., EJN and Frontiers), and was invited as lecturer to many international meetings and has received prestigious scientific prizes (Sackler and Woringer Awards). A young researcher of the group also succeeded to obtain the highly competitive ANR grant for young investigators. Moreover, one young Associate Professor allows the team to be in permanent contact with teaching activities. Thus, the team attractiveness is high and it has strong academic potential.

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

The following achievements can be pointed out to support the group interactions with social, economical and cultural partners:

- Participation to societal and/or public events such as the brain awareness week, Commission of State Department of Science to promote interactions between science, community and policies, Paris Neuroscience Community amongst others.

-The group is also active in motivating private foundations and charities to support research as the team members were successful in obtaining various grants from the following foundations: FRC, FRM, Lejeune and Retina France.

Assesment of the team's organisation and life:

Team 4 is well integrated within IFM, as evident from research collaborations and co-authored papers with other IFM groups. The IFM is an excellent research environment for the team, particularly through the common interests in serotonin, development and plasticity, and mechanisms of psychiatric disorder and it's treatment. During the last programme of research there has been a turnover of staff and students, and all this appears to have been well managed.

Assessment of the team's involvement in training through research

Three PhD, 4 Master-2 and 8 Master-1 students were trained in the team over the elapsed period of time revealing that the group members are active in research training activities. In addition, special interest meetings or events are organized for trainees and high school students; for instance, *Club dévelopment des réseaux neuronaux*, Somatosensory Club, lab visits and introduction to neuroscience. The team leader is the present director of the Paris Neuroscience School (ENP).

Assessment of the five-year plan and strategy

The 5 year plan as set out in the 'Projet scientifique de l'unité' is divided into 2 major projects: (1) Development plasticity of serotonin systems and (2) Activity-dependent and independent mechanisms of visual map formation. These 2 projects are organized into specific and complementary parts involving permanent researchers, students and collaborators from other IFM groups. Moreover, each project largely builds on discoveries made during the last period of assessment, and continues work in areas in which the team leader is a world expert. A third project focused on migration of interneurons was introduced during the presentation of the five-year plan to the committee at the site visit. The committee noted the excellence of the latter proposal on the basis of the presentation, but was somewhat unclear how the 3 projects would integrate, inform and guide each other.

An exciting part of the proposal is the innovative genetic tools that will be applied. This includes the pathway-tracer labeled targeting of 5-HT neuron sub-populations, and 5-HT targeted VMAT2 deletions. It is easy to imagine that high impact findings will come from the use of these models.

On the other hand, a lack of hypotheses and a sometimes less than well defined and broad experimental plans was considered a weakness in the proposal. For example, the 'multiscale analyses of single raphe neurons' is interesting but it may be challenging to decide which candidate genes to target and how to assess their functional effects. Given that the scope of the proposed work looks broad, the committee felt it might be important to introduce a clear strategy to manage the 3 projects over the 5 years of the programme, which would improve the level of integration.

Thus, overall the 5 year plan is exciting and ambitious. It will be important, therefore, to ensure that the experiments are sufficiently resourced if the projects are to achieve a high level of success expected. Bearing in mind that the projects will be under the pressure of international competition, it is possible that either some refocusing and reassessment of priorities, or an increase of the critical mass, may help to make the project a success and achieve it's aims.

Conclusion:

- Strengths and opportunities:

The team leader is a world expert in the reseach topic, and the group has an excellent publication record. The team includes 2 young and active PIs (one full time researcher and one associate professor). The research environment in IFM is very appropriate and the team has developed useful and fruitful national and international collaborations that will certainly help the project implementation and achievement of its objectives.

- Weaknesses and threats:

The current critical mass of the team may not be sufficient to achieve success of all three aspects of the seemingly ambitous project of the group for the next 5 years. The proposed 3 projects are somewhat diverse and it is not clear that they will integrate and inform and guide each other. The team leader will need a strategy to ensure that the above weakness can be overcome or circumvented.

- Recommendations:

Overall the quality of the proposed individual projects is high although the team leader should consider whether it might be appropriate to focus the proposed work on a smaller number of objectives that can reasonably be achieved in 5 years using the resources available to the group.

4 • Team-by-team analysis

Team 5 : Serotonin signaling in plasticity and disease

Name of team leader: Mr Luc MAROTEAUX

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

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	4	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	1	2

• Detailed assessments

Assessment of scientific quality and outputs

During the past 5 years, the research of team 5 has brought about new discoveries and important breakthroughs, particularly in the field of serotonin (5-HT) signaling and its link to depression and impulse control disorders. The group reports 18 peer-reviewed in high impact journals including Nature (x1), Nature Medicine (x1), J. Neuroscience (x1), Molecular Psychiatry (x1), Neuropsychopharmacology (x1). For a relatively small group, this output is impressive, although it has to be stressed that the publications rely mostly on collaboration; the Team leader appears as last author in six publications. Some of the group's most important findings include identification of a genetic variant of the 5-HT2B receptor which is associated with high impulsivity and suicidality in humans, and the demonstration of correlated effects in 5-HT2B mutant mice. Another important discovery is that the 5-HT2B receptor has a role in the positive feedback control of 5-HT neurons, and that this is a key player in the behavioural actions of both antidepressant and psychostimulant drugs.

Assessment of the team's academic reputation and appeal

Team 5 has an international standing in the 5-HT field. The team leader has been invited to give lectures and organise symposia at meetings of international scientific societies (European Behavioural Pharmacology Society, ECNP, Society for Biological Psychiatry, Serotonin Club), and join international scientific committees (IUPHAR Nomenclature Committee). The group is actively involved in numerous national (eg. groups in Paris, Chatenay and Bordeaux) and international (a group at NIH) collaborations. Recent work by the group has been the subject of editorial reviews, and this is further evidence of the high reputation of the group.

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

Team 5 has engaged with the public through interactions with the media, as well as ongoing and past collaborations with the pharmaceutical industry. The group has also been an active partner in European research and training networks.

Assesment of the team's organisation and life:

Team 5 is well integrated within the IFM, as evident from research collaborations and co-authored papers with other IFM groups. The group also contributes to core IFM resources (molecular biology, vecterology). The IFM is a very good research environment for Team 5, particularly through common interests in 5-HT, development and plasticity, and mechanisms of psychiatric disorder and its treatment. During the last program of research there has been a turnover of staff and students, including the arrival of two new permanent members in the group. All of this appears to have been well managed.

Assessment of the team's involvement in training through research

Over the assessment period team 5 has successfully trained a number of research students: 4 PhD and 5 Masters theses have been successfully defended. In addition, group members actively contribute to graduate training through organisation and teaching of workshops, summer schools and other programs. Team 5 has also produced several articles specifically targeted for teaching purposes. Finally the group has participated in a European training network (DEVANX).

Assessment of the five-year plan and strategy

The five year plan of team 5 comprises 3 multidisciplinary research projects, that are linked through a focus on 5-HT2B signalling in the brain. Resolving the properties and function of the latter receptor has been a consistent interest of the team leader since his involvement in the identification of this receptor over 30 years ago. Indeed, the team leader has arguably been the single most important figure in the 5-HT2B receptor field over this time, and his research has underpinned much of what is currently known about this receptor.

Collectively the projects of the team aim to establish the cellular and molecular pathways involved in the behavioural effects of 5-HT2B signalling. A positive aspect is that each project builds on discoveries made during the last period of assessment. One project is focused on neuroimmunology which is a new area for the team. The committee noted that this project is supported by data but that this is preliminary and needs confirmation. In regard to the latter project, it is important that a trained molecular immunologist has recently joined the team. The committee noted that much of the proposed work is in the area of impulsivity and addiction, but that the team lacked behavioural expertise in this area.

The discovery of 5-HT2B effects on 5-HT and dopamine neurons is very interesting. The committee felt that the future proposal would have been strengthened by more experiments aimed to determine the mechanism underlying these effects. An exciting aspect and great strength of the proposed 5 year plan is the innovative genetic tools that will be developed and applied; specifically 5-HT2B knockout in selected cell populations (5-HT neurons, dopamine neurons, microglia). It is easy to see that high impact findings will come from the use of these models.

The committee considered that the proposed research was ambitious and it was not always clear what models and measurements that will be used. This gives a picture of risk, and the need to trust that the team will do the right thing. However, this team has a record of demonstrating that risky approaches pay off. There appears a realistic prospect of the proposed work offering new insights into the pathophysiology of a range of psychiatric disorders. As things stand, it is less easy to see a therapeutic potential in the work as both 5-HT2B agonists and antagonists are associated with unwanted effects that are likely to hamper any clinical development.

Team 5 still has research interests in the peripheral (especially cardiac) actions of 5-HT2B receptors (recent publications, projected funding). It will be important that the combination of CNS and peripheral studies is well managed with priorities focused on the proposed 5 year plan. The committee considered that a case that the peripheral work will benefit the CNS work could have been made.

Conclusion:

- Strengths and opportunities:

Overall, during the past 5 years, team 5 has been very productive and supported by important collaborations. The team has made new discoveries and important breakthroughs, particularly in the field of serotonin (5-HT) signalling and it's link to psychiatric disorder (especially depression and impulse control disorders). This team has a track record of innovative research in the field of 5-HT2B signalling, and this is likely to continue over the next 5 years.

- Weaknesses and threats:

A weakness in the proposal is that it is not always clear what sorts of models and measurements will be used. This gives a picture of risk, and the need to trust that the investigators will do the right thing. However, this group has a record of demonstrating that risky approaches pay off. The committee noted that much of the proposed work is in the area of impulsivity and addiction, but that the team lacked behavioural expertise in this area. The team has research interests in the peripheral actions of 5-HT2B receptors. It will be important that the combination of CNS and peripheral studies is well managed with priorities focused on the proposed 5 year plan. The committee considered that a case that the peripheral work will benefit the CNS work could have been made.

- Recommendations:

Overall the quality of the proposed CNS projects is high. It is recommended that Team 5 intensifies efforts to focus its activities on the CNS work at the expense of cardiovascular projects.

4 • Team-by-team analysis

Team 6 : Neurodevelopmental disorders

Name of team leader: Mr Matthias GROSZER

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	0
N2: Permanent EPST or EPIC researchers and similar positions	1	2	2
N3: Other permanent staff (without research duties)	0	0	0
N4: Other professors (PREM, ECC, etc.)	0	0	0
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	3	3
N6: Other contractual staff (without research duties)	1	1	0
TOTAL N1 to N6	5	6	5

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

• Detailed assessments

Assessment of scientific quality and outputs

The goal of this team is to understand the molecular and cellular mechanisms underlying the establishment of neuronal circuits involved in social cognition and behavior. To address this important scientific issue, the group focus on the study of two transcription factors (TF) (FOXP2 and TBR2), whose mutation can lead to speech and language disorder and to microcephaly and intellectual disability, respectively. The team aims at: i/ identifying the molecular targets of these TF, in vivo from mice models, and in vitro, particularly from human iPSC-derived neurons ; ii/ studying the electrophysiological and behavioral consequences of cerebral cortex-specific deletion of these genes. In order to tackle these issues, the team uses state of the art complementary methods (cell biology, molecular genetics, electrophysiology, etc.) In addition, the group has developed cutting-edge tools, including conditional knockout mouse models and human iPSC-derived cortical neurons. The recent recruitment of an experienced electrophysiologist as a permanent researcher is instrumental to understand how pathological mutations of these TF affect neuron activity. They have also set-up important collaborations at the international level, which is important especially in the context of strong international competition on the FOXP2 side. Overall, the project is highly competitive but feasible. However, the limited size of the group makes it very important to focus on the initial objectives. In the past period the research has been funded appropriately. The two permanent researchers have got a significant number of publications in very good to top journals in their respective fields.

Since his arrival at IFM, the PI took part to international collaborative studies that were published in highest impact journals (Cell, Nature Neurosci) and in other high IF journals (PLOS Genet, J Neurosci, Mol Psychiatry) - but notably, none in first or last position.

Assessment of the team's academic reputation and appeal

The team leader was granted a (possibly five)-years Avenir-ATIP award in July 2010 and was recruited as a permanent INSERM (CR1) researcher in the course of the previous period. He has obtained other grants including one from ANR and one from FRM. This team has national and international collaborations on the FOXP2 project including strong and long-lasting ones in Europe. The team is quite new but several people including several post-docs have already been hosted in the last period and one excellent permanent researcher (CR2 INSERM) was recently recruited, providing confidence concerning the future attractiveness of the group.

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

The PI has been a consultant for a pharmaceutical company. The group has been active in the national part of the Europe-wide public outreach campaign for neuroscience. The licensing of a European patent (biomarkers of neurodegeneration and neuroregeneration) is underway.

Assessment of the team's organisation and life:

The team is composed of two permanent researchers, one engineer, three post-docs and a PhD student. Most of those non-permanent staff members will leave in the next twelve months. How the team will be composed and will organize with respect to the two main goals (Foxp2, Tbr2) is an important point to address in the future. The strong and productive connection with several international groups is a crucial point and must be encouraged.

Assessment of the team's involvement in training through research

Scientific training is ensured through formal teaching program, such as as Master's research program as well as through lectures for Master 2 and PhD students (Paris VI University, Paris Neuroscience School - ENP). The PI also contributed to international training networks.

Assessment of the five-year plan and strategy

This team has a good scientific profile with respect to the objectives. The project addresses several but partially related issues. Indeed the two subprojects of the team rely on overlapping concepts and share some scientific goals and methods. This is particularly important as the team is currently limited in size and some parts of the project are highly competitive. The reviewers acknowledge that the existing collaborative network may partially solve this issue but at the same time the PI should ensure that the activity of the group will lead to a more prominent position of its members in the authorship of the future papers that will come out. Some other issues could be raised: a large number of FOXP2 molecular targets have already been reported and the novelty of the future findings in this case could be questioned, even though this will be done in another biological context; another issue is about the use of iPSCs-derived neurons in the two subprojects, which in addition to being difficult technically might inherently be problematic.

Conclusion:

This team has an excellent scientific profile with regard to various neurodevelopmental aspects and to social behavior. Members of the team have complementary expertises which renders the project feasible - obviously pending that grants are being obtained in the next period. Stable collaborations are already established and the animal and cellular models are available. The group would benefit from being joined by additional members in the near future - the group has been attractive in the past period. The committee believe that it is important that the future data obtained by the team are being published with the PI signing last and corresponding author.

- Strengths and opportunities:

This team has an excellent network of collaborators and is using the appropriate tools. It comprises two young permanent researchers with complementary expertises. The subprojects also look complementary and share overlapping tools and strategies.

- Weaknesses and threats:

The experimental plan is too large and diverse and cannot be accomodated by the rather small size of the future team.

- Recommendations:

This group would strongly benefit from focusing on one single subproject to ensure that it is being productive and that it give rise to publication(s) in the near future.

4 • Team-by-team analysis

Team 7 : Synapses and pathophysiology of reward

Name of team leader: Mr Manuel MAMELI

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

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

• Detailed assessments

Assessment of scientific quality and outputs

The team leader has been in the UMR-S 839 since September 2010. Within that short period he has produced 3 papers that appear to be remnants from his post-doctoral studies and that were published in Nature Neuroscience x2 (1st and 2nd author), and Plos One (2nd author). More recently (2012) he has published a paper in J Neuroscience as last author. In the same period of time he has also written two review articles signed in first and last position as well as a commentary in Science.

At his arrival the team leader was granted a start-up chair of Excellence from the Ecole de Neurosciences de Paris, an INSERM AVENIR grant and city of Paris funding which helped acquire the necessary equipment. In addition he recently benefited from a Fyssen grant to pay for the salary of a post-doctoral fellow.

The team leader has also set up national and international collaborations that should help him perform the intended research projects.

Thus, the team leader has an excellent publication record and a very good international visibility.

All parameters indicate that this is a team leader with a very good previous activity and very high potentials that should be encouraged to pursue on the same path. He was able to successfully conjugate scientific excellence with managerial duties setting up the team. He also seems to benefit from a very favorable environment and from the efficient support from the laboratory director.

Assessment of the team's academic reputation and appeal

From the above, it appears that this young researcher has a know-how in finding funding to set up his research team and that he is very well supported by the local environment. He was able to attract several post-doctoral fellows in a rather short period of time and is publishing his results in top journals.

He has co-organised in 2011 the 2nd IFM colloquium (Paris) and was co-chair of a symposium at the 26th ISN-ESN meeting in Athens.

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

This is a young team not having enough time to establish things in this regard.

Assessment of the team's organisation and life:

The team is composed of only one permanent researcher and two/three post-doctoral fellows. Thus, it is difficult at this stage to analyze its organization's life as a whole. Nevertheless, the presence of such academic trainees and post-doctoral fellows within this team is an indicator of a dynamic and promising young team. The team has a very tight interaction with another team of the same institute both at the technical and scientific levels, including sharing some laboratory space and equipment, which favor the translation of expertise between the teams and a very good training environment for the PhD students and trainees.

Assessment of the team's involvement in training through research

In a short period of time the team has trained one undergraduate and one Master's student. Three post-docs have joined the team. The team leader has recently obtained his HDR, which will allow him to have PhD trainees under his direct supervision.

Assessment of the five-year plan and strategy

The team aims to dissect brain circuitry involved in salience processing mainly using electrophysiology and focusing on the habenula brain region, which provides a scientific niche to explore. Aim 1 is focused on synaptic transmission and plasticity in the lateral habenula (LHb) while aim 2 is directed towards synaptic correlates between the LHb and aversive/rewarding processing. Thus the scientific project seems to be quite focused and within the expertise of the team.

The team leader is well aware of limitations due mainly to the size of the team and is setting out to seek european fundings (ERC) as well as national major fundings (ANR) to fulfil his goals, and recruit post-doctoral fellows as well as a PhD student. Given his previous success and the scientific potential of the team one can be quite confident that the probablilty of success in obtaining funding will be high.

The Institute Fer à Moulin seems to be the perfect place for this young team and should significantly help the team leader acquiring the necessary managerial expertise to fulfil his aims as several senior scientists with international reputations are already present within this Institute.

Conclusion:

- Strengths and opportunities:

This is young motivated team that is very well funded. The team benefits from the favorable local environment and from the strong support of the head of the institute. The team leader has an excellent publication record and is already visible at the international level despite his young age.

All major necessary equipment to achieve the proposed project has been either acquired or is already present at the host Institute.

- Weaknesses and threats:

The main weakness lies within the size of the team with only one permanent researcher. Another threat comes from the funding agencies and the success rate of grant proposal. However, given the publication record of the team leader and his previous success in obtaining funding one can be optimistic.

- Recommendations:

At the mid-term of the coming review period, trying to attract another full time INSERM/CNRS researcher within this team should prove to be very helpful in consolidating the team and fulfilling the research projects.

5 • Conduct of the visit

Visit dates:

Start: "Thursday the 7th of February 2013", at "9:00"

End: "Friday the 8th of February 2013", at "18:00"

Visit site(s): Insitut de Fer à Moulin

Institution: INSERM/UPMC

Address: 17, rue Fer à Moulin, 75005, Paris.

Conduct or programme of visit:

The visit took place within the IFM, during two full days in early February 2013. After a general introduction by the AERES representative and the chairman, a 30 min general presentation of the unit by the future director was given in the presence of most of the group leaders and some additional personnel of the unit, followed by 30 min discussion. Each group leader presented the past activities and projects for 25 min followed by 25 min discussion in the presence of the team members and the director. The director and team members left the room 5 min before the end to allow a "private" discussion between the AERES committee members and each group leader. Then 5-10 minutes discussion was allowed between the AERES experts to discuss and evaluate the quality of the team on the 6 different aspects requested by the AERES. The committee was split into three groups each having one hour discussion with i) the students and post-doctoral fellows, ii) the researchers with permanent position, excluding the team leaders, and iii) the technicians and engineer staff. Half an hour exchange with the representatives of the Pierre et Marie Curie University (UPMC) and INSERM took place the last day, before the final door closed meeting. Finally, at the end of the visit, a door-closed meeting was conducted to qualify each team being evaluated.

A representative of the technical staff of INSERM (CSS6) was present on site during the visit. He attended the presentation and discussion of most teams, but did not participate in the discussion. He organized a general discussion with the Engineers and technicians, in preparation of the one with the AERES committee representatives.

Specific points to be mentioned:

The president wishes to thank all experts from the committee for their very active participation during the discussion, their constructive questions and remarks to the team leaders, bringing about a very nice human and scientific atmosphere, optimal for such a unit evaluation.

The committee regrets to not have had the possibility to visit the laboratory and the platforms during the visit (in particularly the animal facility).

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

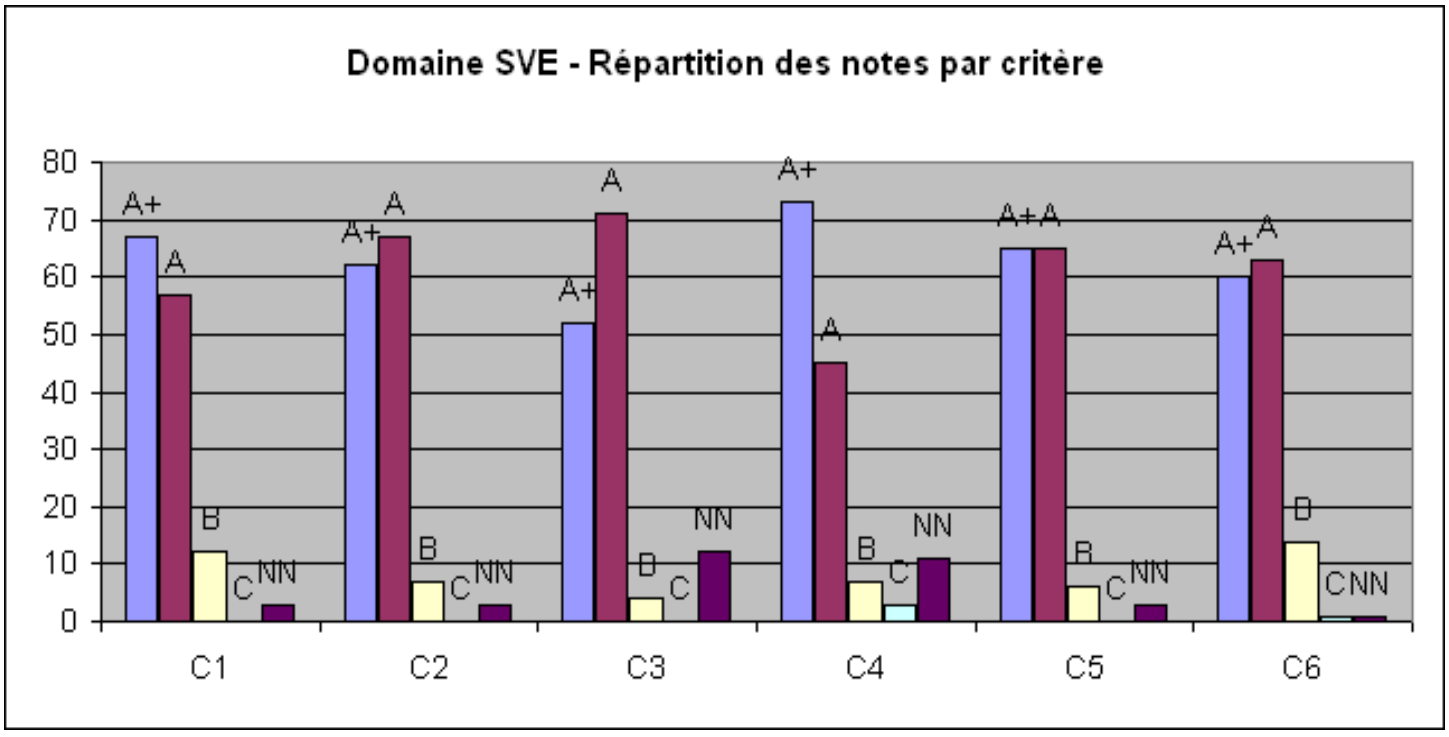
Grades

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 25 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 Fer à Moulin, porté par M. Girault. 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

Comments on the 2013 AERES report for the *Institut du Fer à Moulin* - UMR-S Inserm UPMC 839

The current director and vice-directors, the team leaders and all the personnel of the IFM thank the AERES committee members for their time and thorough analysis of our Institute, as well as for their very positive overall evaluation. We would like to address a few point raised by the committee that may require some clarification.

General comments

1- Renovation of the animal facility

The committee was concerned by "the anticipated difficulties that will be encountered by the IFM groups during the constructions which will result in a complete closure of the facility for up to a year, whereas experiments with mice are an essential part of their activity". The committee also noted that the IFM personnel in general worried about this period. It concluded that "It is critically important to resolve the current situation regarding animal maintenance and breeding, otherwise, many of the projects will be seriously challenged."

We share these concerns and we have carefully planned, with the support of Inserm, all the necessary actions to minimize the perturbations and delays to our research activities during the renovation of the animal facility. This strategy was not detailed to the committee since we had not anticipated that it would be a topic of interest. The measures taken are as follows:

- A dedicated work group (including the animal facility manager, the facility scientific director and two senior scientists, with the active participation of the director) is in charge of anticipating, planning, and managing the construction phase.
- Prefabricated animal housing modules have been purchased and set up at the IFM site. They are currently being put into function. The capacity will be about 400 cages. Appropriate ventilated racks and disposable cages have already been purchased. The current personnel of the animal facility (1 manager, 3 technicians) will be devoted mostly to the functioning of this transient facility and will be provided with offices on the ground level of the IFM main building during this period.
- Some activities will be transiently carried out in the IFM building (e.g. perfusion and tissue preparation).
- Agreements have been concluded with two other large and recently renovated animal facilities within the UPMC animal facilities network (including one at the Pitié-Salpêtrière within walking distance from the IFM) to house clean mice for the IFM and to carry out behavioral and surgical experiments.
- "Rederivation" of mouse lines to eliminate pathogens by embryo transfer has been started (approx. one half of the lines are already clean and currently housed in SPF facilities at the CDTA (Orleans) or CERFE (Evry).
- Updates are discussed at monthly team leader and IFM council meetings, as well as animal house facility user meetings, and when necessary announcements are made before the weekly Progress Reports to update all personnel and discuss any new concerns.

Altogether, these various procedures are already either well initiated or planned in details to be put into action as soon as the construction actually starts.

2- Critical size of some teams

The committee noted that "the small size of some teams makes the feasibility of projects vulnerable" and recommended that "the IFM leaders define a clear strategy to solve questions related to the critical mass of several teams".

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www.upmc.fr

It should be emphasized that the proposed teams for the next five years include 3 “senior” teams and 4 current or former Avenir groups (i.e. competitive support for young investigators). The two former Avenir groups now include several persons with permanent positions: proposed Team 2 (Francis & Goutebroze) includes 4 CNRS scientists, 2 lecturers (UPMC MCU), 2 technicians ; proposed Team 3 (Poncer & Lévi) includes 1 Inserm and 1 CNRS scientists and an Inserm “study engineer” (IE). A UPMC lecturer will be recruited before the end of 2013. The two current Avenir groups are smaller since they were created more recently. The “older” one, Team 6 (Groszer), was recently joined by a newly recruited Inserm scientist (CR2).
In general the IFM teams comprise a significant proportion of young scientists of international origin, including graduate students and post-docs. This is, in our opinion, a clear sign of dynamism and success and puts these groups on par with the international competition. We want to stress that the IFM scientists and teams have been very active and efficient for recruitment since the creation of the Institute with 3 CR2 and 2 CR1 positions at Inserm and 4 lecturer positions at UPMC. One excellent candidate applies for an Inserm position this year and 1 lecturer position is open for recruitment. Given the size of the IFM and the scarcity of positions this rate of recruitment can be considered as excellent.
In addition, three scientists (CNRS CR1) who already had positions have joined the IFM since its creation. Twelve technical and administrative staff members have been recruited including 8 people moving from other laboratories and 4 with new Inserm positions. Unfortunately this category of personnel has also decreased at the same time due to retirement and people who moved to differentcities for familial reasons. With support from Inserm, we try to maintain an appropriate researcher: technical and administrative staff ratio.
Strategy to solve questions related to the critical mass of several teams:
We have already encouraged fusion of groups when it had a strong scientific rationale and will continue to do so. We encourage young scientists with appropriate profile and curriculum to apply for positions at Inserm. We hope to have a continuous support from the UPMC for obtaining lecturers positions. Finally, we encourage scientists with positions who are interested by research carried out by IFM teams and who would clearly bring additional and complementary expertise to join us (this recently is the case for one behavioural scientist who will join in 2014).

3- Translational aspects

The committee noted that “Translational aspects of many of the projects are still at an exploratory stage” and recommended that “the IFM improves translational aspects of its research by building collaborations with neurologists and psychiatrists”. The committee underlined however that “An excellent opportunity for such developments is offered by the Labex Bio-Psy initiative, for which the institute’s director is the coordinator and scientific director.”

The teams already have ongoing collaborations with neurologists (3), geneticists (3), and psychiatrists (2), which were not extensively described given the limited time for team presentations. In addition there is a group currently co-headed by a neurologist (Pr. Hugon), who is not part of the application since he will move to a location closest to his clinical department but with whom collaboration will continue (joint ANR grant). As rightly underlined by the committee, the Bio-Psy Labex will be used to foster additional collaborations with clinicians. In fact, this was a major motivation behind this project: to facilitate the openings towards translational research.

4- Behavioral scientist

The committee pointed “… a need of [behavioral scientists] in the IFM. One senior scientist-level expert in mouse behavioural studies has already been recruited at the IFM, but given the size of the institute and volume of research proposed, additional recruitment is needed.”

As pointed out the recruitment already carried out in Team 2 addresses this point. Until now several senior scientists at the IFM, although not being “pure behavioral experts” had sufficient experience to successfully carry out relevant research. In addition the teams have benefited from the contribution of

several experimented senior post-docs, who were recruited for their expertise in this area. In the future we will attempt to recruit another tenured behavioral scientist (e.g., see Team 5). Finally when we open a call for a new team, as anticipated, we will consider the opportunity of recruiting an expert in behavior.

5- Additional points

- A meeting with lecturers has already been organized, following the committee's recommendations, and will be regularly scheduled. It has already brought interesting ideas and proposals.
- The ways to focus research of specific teams according to their current work force has already been discussed with concerned team leaders (see specific comments).

Specific comments on teams' evaluations

Team 2 Fiona Francis & Laurence Goutebroze

Concerning Project 2 (iPSCs), the committee suggested "putting significant effort toward the exact experiments planned with hiPS cells as 1/hiPS handling is tricky and time-consuming; and 2/the lab does not seem to currently master such technology."

As emphasized in the Team 2 presentation, for Project 2 we are primarily focusing on the use of mouse models to study Caspr2 function and mutations. We also mentioned in the written version of the project, but did not have time to discuss in detail during the presentation, that we are considering the generation and study of hiPS cells from patients as an alternative model. This exploratory iPSC work has been discussed with our clinical collaborators in the framework of the Bio-Psy Labex project. We fully agree that this part of our future work requires careful consideration and planning, and expertise from collaborating groups who have established experience in this area.

Team 3 Jean-Christophe Poncer & Sabine Lévi

We thank the committee for its enthusiastic evaluation of our achievements and projects.
Regarding securing the position of our senior postdoc, we agree with the committee that this should be a priority as several of our current projects rely on his expertise. A lecturer (MCU) position was recently obtained from UPMC and this talented young scientist is now applying for this position. Alternatively we will explore possibilities to extend his contract on team funding (despite the limitations imposed by new regulations on postdoctoral contracts).
The committee also expressed concerns about future funding of the team. In this respect, we recently were awarded a collaborative Research Grant from the Human Frontier Science Program, which will secure funding of the team for at least the next 3 years. Other grant applications are pending.

Team 4 Patricia Gaspar

We would like to stress important aspects of publications and team organization that may have not been sufficiently clearly presented to the committee.
Publications: The total number of publications is 29 and not 17 as indicated in the report, if one takes into account all the publications of the team members with permanent positions, including several important publications made when these investigators were at the IFM. Thus, from 2008 to 2013, the 4 current team members with Inserm or UPMC positions produced 19 original publications including 1 Neuron, 1 Developmental cell, 1 Plos Biology, 1 Neuropsychopharmacology, 7 in J Neuroscience , 1 Development. Furthermore, 10 reviews or commentaries were produced by the team including 1 Trends in Pharmacological Science, 1 Philosophical Trans, 1 commentary in Science, 1 in Cell, and 1 in Neuron.

Team organization: Importantly, one senior PI, Christine Métin has joined the team recently. Please note that Christine Métin was initially thinking to reapply with her current team contours. This project turned out not to be possible, due to the unanticipated leave of the team co-leader (R.M. Mège). Therefore given the very short notice before the AERES application, she in agreement with Patricia Gaspar who had been working with her previously, decided to join forces with team 5. This decision was strongly grounded scientifically, but could not be detailed in the written application due to its extremely recent date. Perhaps the team did not make these circumstances sufficiently clear to the committee. Besides, a junior Inserm scientist, Alexandra Rebsam was granted a junior ANR award to develop her project. The latter project stemmed out from the main project of the team to become an independent project.
Coherence of projects and strategy: *The committee noted that "it was somewhat unclear how the 3 projects would integrate, inform and guide each other".*
The individual projects are carried out by 3 principal investigators with internationally recognized expertise in their subfields: Christine Métin in neuronal migration, Alexandra Rebsam in visual system development, and Patricia Gaspar in serotonin system development. All 3 projects pertain to the larger field of neural circuit development. They are definitely already informing and guiding one another since they share common concepts and molecular mechanisms. Furthermore the 3 projects involve very similar experimental / technical expertise, which is a true asset for the team.

Team 5 Luc Maroteaux

The committee noted that "much of the proposed work is in the area of impulsivity and addiction, but that the team lacked behavioural expertise in this area."
It should be noted that the trained personal (postdocs) that have been implicated in these studies recently left the lab after having trained students in the relevant experiments. The team leader is also in the process to attract a tenured, trained person in the behavioral field.

The committee considered that a case that the peripheral work will benefit the CNS work could have been made.
The short time allowed made it difficult to recapitulate the complete background behind the proposed work. It is clear that much of the team work initiated at the CNS levels was supported by previous "peripheral" observations by the group leader (e.g. lack of response the serotonin releasers, anorexigens or ecstasy). Similarly, the team's recent observation that serotonin is critically involved in hematopoietic lineage including monocyte/macrophages is part of its recent interest toward serotonin action on microglial cells (resident macrophages of the brain).

"It will be important that the combination of CNS and peripheral studies is well managed with priorities focused on the proposed 5 year plan. It is recommended that Team 5 intensifies efforts to focus its activities on the CNS work at the expense of cardiovascular projects."
Again, the lack of time precluded a detailed presentation of the planned evolution of the team research.
It is clear that the former research activity outside the CNS is being progressively reduced (and was actually only very briefly mentioned in the presentation). This will indeed allow the team to fully document the recent original observations made in the brain concerning the contribution of the 5HT-2B receptor to 5-HT neurons, dopamine neurons, and microglia.

Team 6 Matthias Groszer

We thank the committee for the valuable suggestions and we address certain issues raised below.
Publications:
The committee believes that it is important that the future data obtained by the team are being published with the PI signing last and corresponding author.

The group has finished experiments for two ambitious projects addressing Foxp2 and Tbr2 functions in vivo and manuscripts are currently being written. The single first authors of each paper will be Postdocs from the team (Foxp2: C. Mombereau + 3 team members as co-authors; Tbr2: T. Ghosh + 1 team member as co-author). The PI is signing as single corresponding last author.

Group size and scope of projects:
Most of those non-permanent staff members will leave in the next twelve months. How the team will be composed and will organize with respect to the two main goals (Foxp2, Tbr2) is an important point to address in the future.
One new post-doc applicant with a background in behavioral studies has just submitted fellowship proposals. An ANR grant including a post-doc position is under review. Another scientist with extensive training in iPSC technology during his thesis (2012) is seeking post-doc funding to join the lab. We also increase our efforts to attract tenured personnel with background in genomics/bioinformatics.

This group would strongly benefit from focusing on one single subproject to ensure that it is being productive and that it gives rise to publication(s) in the near future.
We will strengthen our focus on transcriptional regulation for social brain development, a relatively new topic in the field of molecular genetics. As molecular entry point we continue work on the transcription factor Foxp2 in neural circuits mediating social behaviors and Foxp2 related gene networks which emerge from current large scale human genetic studies. At the technical level, we have established a number of new tools to be competitive (mouse lines, bacTRAP in vivo circuit-specific transcriptional profiling, iPSC technology and electrophysiology). There is a critical mass of international collaborations and it dovetails into the orientation of the IFM towards neuropsychiatric disorders in the context of the Bio-Psy Labex.

Some other issues could be raised:
A large number of FOXP2 molecular targets have already been reported and the novelty of the future findings in this case could be questioned, even though this will be done in another biological context;… Another issue is about the use of iPSCs-derived neurons in the two subprojects, which in addition to being difficult technically might inherently be problematic.
Hundreds of potential FOXP2 targets emerge from experiments in transfected cell lines and tissues; a few have been associated with autisms and other neuropsychiatric disorders. Our studies directly dissect targets in specific circuits and developmental stages in vivo, and their contribution to social behavior. We have established iPSC technology in the lab and acquired funding based on our preliminary results. To optimize resource allocation, for the generation/maintenance of iPSC cell lines from patient samples we collaborate with the iPSC laboratory of Dr. Annelise Bennaceur Griscelli (Inserm U935, Villejuif), a highly experienced lab in this area. We focus on the guided differentiation of these iPSCs into cortical and striatal neurons. This work is essential to identify relevant Foxp2 targets from our mouse studies, since this transcription factor carries human specific amino acid changes which are expected to cause differences in transcriptional regulation between both species.

Team 7 Manuel Mameli

We appreciate the comments of the committee. Although the team size could be seen as a weakness, the team has been established recently, at the end of 2010. We foresee that, after more funding is secured, another or two new members will join the laboratory. In this context, we will work toward the recruitment of a permanent researcher in the team allowing to develop the projects we proposed for the following five years.