Département neuroscience

Rapport Hcéres

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

Research Units Department

AERES report on unit:

Neurosciences Department

Under the supervision of the following institutions and research bodies:

Pasteur institute

INSERM

CNRS

May 2012

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

Unit

Name of unit:	Neurosciences Department
Acronym of unit:	
Label requested:	
Present no.:	
Name of Director (2009-2012):	Mr Jean Michel HEARD
Name of project leader (2013-2017):	Mr Thomas BOURGERON

Members of the committee of experts

Chair:	Mr Stéphane OLIET, Bordeaux
Experts:	Ms Claudia BAGNI, Leuven, Belgium
	Ms Francine BEHAR, Paris (CSS Inserm Representative)
	Mr Stéphane DIEUDONNE, Paris
	Mr Thomas JENTSCH, Berlin, Germany
	Ms Isabelle MANSUY, Zurich, Switzerland
	Mr Antonio PERSICO, Roma, Italy
	Mr Martial RUAT, Gif sur Yvette (CoNRS representative)
	Mr Claudio STERN, London, United Kingdom

Representatives present during the visit

Scientific Delegate representing AERES:

Mr Pierre LEGRAIN

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

Ms Catherine LABBE-JULLIE, INSERM

Ms Nathalie LERESCHE, CNRS

Mr Tony PUGSLEY, Pasteur Institute

Report

1 • Introduction

Date and conduct of visit:

The visit took place on May 14 and 15 at the Pasteur Institute in Paris. The meeting started with welcoming remarks by Alice DAUTRY, and Tony PUGSLEY, respectively the General Director and the Scientific Director of Pasteur Institute. Next, Thomas BOURGERON, the acting director of the Department of Neuroscience, gave a general presentation for 30 minutes. This was followed by presentation made by each of the 8 teams that were applying for the AERES evaluation. The length of these presentations varied according to the size of the team from 45 minutes (20' talk, 25' questions) for the smallest, 70 minutes (35'+ 35') for most teams, up to 90 minutes (45' + 45') for the largest. A visit of some of the laboratories was organized the first day. Meetings with the different categories of personnel (60') including permanent staff scientists, students and postdocs, as well as technicians and engineers were organized on the 1rst day. The committee finally met for 15-20 minutes with the representatives of the different organisations including Tony PUGSLEY for the Pasteur Institute, Nathalie LERESCHE for the CNRS, Thomas BOURGERON as director of the department and Pierre-Marie LLEDO as head of the URA CNRS 2182. At the end of these 2 days of presentation, the AERES committee members had a closed-door meeting.

History and geographical location of the unit, and overall description of its field and activities:

The Department of Neuroscience of the Pasteur Institute was founded in 2002. It is presently composed of 7 independent teams for a total of about 100 persons. The scientific activities of the department range from fundamental research to clinical trials, all related to the field of Neurosciences.

The project includes the creation of a new team to bring the number of teams to 8. Most teams are located in the Fernbach building except E5 and E8. The size of the teams is very heterogeneous ranging from small (E8; 3 individuals) to very large (E1; about 44 individuals).

The organization of the department is quite complex in the sense that 5 of the teams (E2, E3, E4, E6 and E7) form collectively a CNRS unit (URA 2182) whereas E1 and E5 form two distinct Inserm units (U587 and U622, respectively).

Management team:

The director, Thomas BOURGERON has been recently appointed (end of 2011) and is assisted by a deputy Director, Uwe MASKOS. The director is interfacing directly with the direction of the Pasteur Institute on a regular basis. A department bureau that includes all team leaders is supposed to address the scientific policy and the future orientations of the department.

Unit workforce:

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers****
N1: Professors or assistant professors	10	10	10
N2: EPST or EPIC researchers	15	16	16
N3: Other professors and researchers	14	15	15
N4: Engineers, technicians and administrative staff *on a permanent position	23	22	
N5: Engineers, technicians and administrative staff * on a non-permanent position	7		
N6: Postdoctoral students having spent at least 12 months in the unit	24		
N7: Doctoral students	14		
N8: PhD defended	12		
N9: Number of Habilitations to Direct Research (HDR) defended	4		
N10: People habilitated to direct research or similar	17	14	
TOTAL N1 to N7	**107**	**63**	**41**

* **If** different, indicate corresponding FTEs in brackets.

**Number of producers in the [01/01/2007-06/30/2011] period who will be present in 2013-2017.

Definition and downloading of criteria:

http://www.aeres-evaluation.fr/Evaluation/Evaluation-des-unites-de-recherche/Principes-d-evaluation.

2 • Assessment of the unit

Overall opinion on the unit:

The research activities of the department cover different aspects of Neurosciences, from basic to translational research, such as neurotransmission, synaptic plasticity, neurogenesis, myelination and pathology including neurodegenerative diseases, autism, auditory deficits and nicotine addiction.

The overlapping interests provide grounds to active collaborations between the groups. Thanks to the involvement of clinicians, some of these topics have very important medical outcomes in terms of diagnostics and innovative therapies.

For historical reasons, this department was built on a very competitive research in the fields of ligand-gated ion channels and later on cochlear physiology and pathophysiology. Along the years, additional topics have emerged, by the addition of new groups interested in neurogenesis, neurodegenerative diseases, autism but also synaptic plasticity. Every team activity is directly related to at least one pathological condition, even though each team develops a strong basic research.

A major factor of the department is its ability to go from molecular to behaviour mechanisms and human pathologies encompassing all the levels of analysis in neuroscience. Various and complementary methodological approaches available in the department are used in animal and human studies. This includes molecular and cell biology, biochemistry, crystallography, in vivo and in vitro electrophysiology, cell imaging, behaviour, lentiviral vectors, transgenic animals, cell therapy and genetics.

Strengths and opportunities:

The committee of experts noticed the following assets:

- Excellence of the research

- A real capacity to recruit new teams with excellent investigators

- Attractiveness for international and talented postdoctoral fellows

- A real capacity to obtain external funding and to participate to, and coordinate, major international networks

- A very strong support from the Pasteur Institute for new arriving teams

- Access to technical platforms within the department and on the campus

- Development of state-of-the-art techniques (STED microscopy, lentivirus platform, olfatometers…)

- A real bench to bed type of research that associates neuroscientists with ENT (Ear, Nose and Throat) , specialists and ophthalmologists, neurologists and psychiatrists; on-going clinical trials for cell therapy

- Very good interactions between some of the teams

- A good cocktail of senior and junior teams that mixes dynamism with experience

Weaknesses and risks:

The committee of experts has nevertheless detected several weaknesses:

- The dynamics of the department is weak. Right now, teams requests go directly to the Pasteur direction, thereby not contributing to the cohesion of the department

- There is no real identity of the department. For instance, the webpage has not been updated for several years, there is no common use of a general emailing announcing the seminars nor the journal clubs, no meetings with the different categories of personnel.

- Having several sub-groups (URA CNRS and Inserm Units) within the department does not help for its dynamics or for its cohesion.

- The restriction in size and space and human resources imposed by the Institute is limiting the development of the teams regardless of their quality.

- The restriction in size limits the number of PhD students since PI preferences usually go to experienced postdocs. As a consequence, training of students and diffusion through training is limited.

- The budget of the department is limited preventing the occasional support of specific projects or personnel

Recommendations:

The committee of experts makes the following recommendations:

- Improve the dynamics of the department by organizing meetings on a regular and frequent basis with all the group leaders and by making sure that decisions impacting the department are taken at that level. All decisions or requests from individual teams should be first discussed and arbitrated at the department level before reaching the direction of the Institute.

- Obtaining human resources for the platforms that would be administratively attached to the department and not to a specific team

- General emailing, advertising all departmental activities, should improve communication within the department

- The website should be updated on a regular basis

- Meetings with representatives of the Department personnel should be organized

- A departmental journal club should be created. All activities that will bring together the entire department would be an asset.

- All the teams (except for clinicians) should be in the same building to improve collaboration and sharing the resources.

- A more consequent budet should be allocated to the director to support when required projects or personnel.

- Large-scale data analysis is lacking and is very much in demand by several teams. The committee of experts recommends funding such a core-facility.

3 • Detailed assessments

Assessment of scientific quality and production:

All the group leaders have international recognition in their field, and are regularly invited in international and national meetings and conferences. The overall productivity is outstanding, probably among the best for neuroscience institutes in France considering the size of the department. Specific assessment of the scientific production is made on a team-by-team basis in the following chapter.

Assessment of the unit's integration into its environment:

The teams that compose the department are all involved in top network, locally, nationwide or international, many of them as coordinators.

The teams of the department benefit from several grants from different sources, locally from the Neuropole, RTRS and RTRA, nationally with many ANR (19), FRM (1 FRM team), Labex (4), Carnot Institutes (1), and internationally with participation to several European FP7 consortiums, ERANET, ERC (1) and ITN grants.

The industrial collaborations and transfers are also very good as reflected by the number of contacts with different companies and some patents.

Assessment of the research unit's reputation and drawing power:

Members of the department have been the recipient of many different prizes and awards including the Alfred Fessard lecture, awards from the French academy of Science (2), from the FRM (Camille Woringer), Grand prix Inserm de la Recherche Médicale and the Pasarow Medical Research Award in Neuropsychiatry.

Most group leaders are invited on a regular basis to international events (symposium, workshop, schools) in their respective field of expertise.

The attractiveness of the department and of the group leaders abroad is important as revealed by the presence of several foreign students and postdoctoral fellows, some of them funded by very prestigious international agencies (HFSP, EMBO, Marie Curie). Many postdoctoral fellows that worked recently in the department have now set up their own laboratory elsewhere.

The committee has noticed the low number of PhD students compared to the available supervising possibilities. This is an indirect consequence of the human resources limitation imposed by Pasteur Institute on the teams.

Due to the excellence of the research carried out by the different teams, many collaborations were developed with foreign laboratories all over the world.

Assessment of the unit's governance and life:

A director assisted by a deputy director is responsible for the governance. The director is new but he is a leader in his field and should be able to impose his own vision and strategy for the future. The governance, and more importantly the dynamics of the department, needs to be improved. The budget allocated by the direction allows the organisation of seminars and of an annual retreat. The real influence of the department direction on the decisions impacting the life of the department and the scientific strategy is not very strong. It appears that the teams are directly dealing with the direction of Pasteur Institute and that not so many decisions, if any, are taken by the department head. Allocation of resources and space for instance, should be the prerogative of the department that needs to identify its own priorities. Right now, the department director can only organize seminars and a retreat with his allocated budget.

Meeting with the different categories of personnel also revealed a deficit in communication within the department. Seminars should be actively advertised to the entire personnel through general emails. More meetings with the representatives of the personnel should be organized to listen and resolve local problems, including specific meetings for technicians and engineers. Similarly, a general procedure regarding authorship for technicians should be imposed for the entire department. Finally, the department website is out of date, which is not what one would expect from such a prestigious Institute.

The URA CNRS 2182 constitutes the core of the department. It is at the origin of many of the technical platforms. The teams are all interested in synapses and neurotransmission. They thus form a coherent group in which the teams interact a lot with each other. The department benefited a lot from the existence of the URA CNRS in terms of team collaboration, sharing facilities, resources and expertise, developing platforms and federating several teams. The committee of experts thinks it is now the responsibility of the head of the department to bring this operating mode to the level of the entire department.

Regionally, the teams are deeply involved in structuring research and education in Neuroscience through their participation to RTRS, RTRA, Neuropole and ENP. Some team members have key positions in these networks.

Assessment of the strategy and 5-year project:

There is a very strong scientific project that is aimed at increasing our knowledge on connectivity in the nervous system and on sensory systems. More specifically, the objectives are to identify the basic mechanisms underlying normal connectivity dynamics and their defects in diseases, and to develop project with potential impacts on medicine. Accordingly, this proposal is extremely relevant for many neurological and psychiatric disorders, including nicotine addiction, neurodegeneration, auditory deficits, depression and autism.

There is a clear will to develop the department which is shared by the direction of Pasteur Institute and of the department. Recruiting additional teams is also a recommendation from the committee of experts if the Pasteur Institute wants to maintain its national and international recognition in the field of neurosciences.

3 new teams should be recruited soon (less than 18 months). The teams in the department have identified the fields they would like to be covered by the new teams. This includes expertise not yet present in the department such as proteomics of the synapse, modelling and cortex network specialists. It is not clear whether this is the best strategy to attract top senior scientists. The committee of experts suggests having a more open call with suggestions about the fields that need to be covered rather that imposing them.

The feasibility of the scientific project is extremely high, thanks to the expertise and excellence of all the groups. Overall, there is a large number of original and cutting-edge research projects that are described in details in the team-by-team analysis.

Assessment of the unit's involvement in training:

Several members of the department are strongly involved in teaching activities. The department every year provides a 6-weeks advanced undergraduate course in neuroscience to student from the University of Paris 6, Paris 7, the Ecole Normale Supérieure and the Ecole de Medecine of Inserm. Clinicians are involved in the organization and in the teaching at medical schools (Paris, Bordeaux). They also participate to professional training courses like those designed for teachers of deaf children and speech therapists.

One of the group leaders holds a Chair at the Collège de France, giving annual series of lectures and seminars. Some of the scientists of the department actively contribute to worldwide courses including the responsibility of a course at Cold Spring Harbor Laboratories and of a Boston-Paris internship program in molecular biology. The department is also involved with the Paris School of Neuroscience (ENP) that enables sharing rotating PhD students.

The PhD students present at the meeting gave a very positive judgement of their PhD program, of the collaborative atmosphere present in the Department between permanent and non-permanent personnel and in between the different teams, of the technological platforms available, of the seminars and the retreat. Only few minor points were raised, primarily representing issues that could be further improved but do not represent major problems. This includes:

- The strict rules and regulations implemented by the Pasteur Institute discourage universities from organizing seminars, courses or events at the Pasteur Institute. This brings about a sense of relative isolation, especially for PhD students;

- A common journal club open to all members of the Department (or at least of members of the five CNRS teams) is typically attended by members of 3 teams only, but not by members of the other CNRS or Inserm teams. It would be good to have a common journal club series.

- There is no departmental mailing list, no updated departmental web site, no common directory through which members of different teams can exchange large files at ease.

- Postdocs view the “Research in Progress” seminars very favourably and in their mind they should be organized more frequently, in order to give everyone an opportunity to present his/her data and to get trained at giving lectures before being exposed to international meetings.

In summary, the overall judgement of PhD students (many coming from France, but some coming from the USA or the UK) was very favourable, also in comparison with well-renowned foreign institutions. Also post-docs were very happy and described the environment as rich of opportunities, very well equipped, and highly collaborative at their level. The points raised above would further improve an already positive and constructive climate. Finally, some of those points must be viewed within the broader framework of a relatively weak departmental structure, which is a general comment the committee of experts raised at multiple levels.

4 • Team-by-team analysis

Team 1: Genetics and physiology of hearing

Team leader: Ms Christine PETIT

Workforce

Workforce	Number on 06/30/2011	Number on 01/01/2013	2013-2017 Number of producers**
N1: Professors or assistant professors	5	5	5
N2: EPST or EPIC researchers	7	7	7
N3: Other professors and researchers	9	9	9
N4: Engineers, technicians and administrative staff *on a permanent position	8	8	
N5: Engineers, technicians and administrative staff * on a non-permanent position	2		
N6: Postdoctoral fellows having spent at least 12 months in the unit	10		
N7: Doctoral students	3		
N8: PhD defended	5		
N9: Number of Habilitations to Direct Research (HDR) defended	3		
N10: People habilitated to direct research or similar	7	7	
TOTAL N1 to N7	**44**	**29**	**21**

In 2006, when the research unit Inserm UMRS587 was granted renewal, it was made up of three groups, « Team 1 » Genetics and Physiology of Hearing (Génétique et physiologie de l'audition) based at Institut Pasteur, « Team 2 » at Armand Trousseau children hospital, as well as « Team 3 » at Victor Segalen Bordeaux-2 University.

• Detailed assessments

Assessment of scientific quality and production:

This team is without doubt one of the world leaders in hearing research. In the past, its main line of research was the identification of the many genes involved in genetic hearing loss. By collecting, together with their collaborators, a large number of families affected by different forms of hearing loss (e.g. classified as to mode of inheritance, onset etc.) and using e.g. linkage analysis and sequencing techniques, this team was able to identify a number of genes underlying inherited hearing loss in humans. This work continues in a fruitful collaboration with a group located at the Trousseau Hospital in Paris that is part of the Inserm UMRS-587. This predominantly clinical group is mainly involved in the recruitment and characterization of patients with hearing loss, human genetics, and therapy. A particular focus is on different forms of Usher syndrome, which is associated with deafness and blindness. The team 1 now extends its research into the area of blindness, which profits from a collaboration with the Vision Institute in Paris. Although many human deafness genes have already been discovered, in part by this laboratory, many genes remain unknown and the complexity of the inner ear and the hearing process suggests that many more will be found. Undoubtedly, the pace of gene discovery will be vey much accelerated by next generation sequencing techniques, which the team is not carrying out within Pasteur Institute, but with a company as paid service.

The discovery of new deafness genes is not only of evident medical importance, but also allows to disentangle the cellular mechanisms involved in hearing. This, however, requires an interdisciplinary approach involving a broad arsenal of morphological, biochemical, and biophysical techniques, as well as the generation of mouse models. Over the past decade or so, the group leader has wisely expanded her methodological spectrum in order to really understand in detail how the individual molecules, many of which are encoded by human disease genes, interact and form functional units. Beautiful examples include the elucidation of complexes involved in mechanosensation at the hair bundle. This lab has also expanded into electrophysiology, in part by sending postdocs abroad to other laboratories to learn specialized patch-clamp techniques. A small electrophysiology group within the team has been established at Pasteur. In addition, there is a very productive collaboration with a “satellite” of the team located at the Université Bordeaux Segalen in the framework of the Inserm unit 587. The group in Bordeaux is particularly interested in the synaptic transmission at sensory hair cells, which, like photoreceptors, have special ribbon synapses. This work, which involves electrophysiology, ion imaging and immunohistochemistry, is of high quality and constitutes a valuable addition.

The unit is extremely productive, not only concerning the number of publications, but above all in terms of their quality and impact on the field. The PI and her team have published 130 papers from 2006 to 2012. Among those papers are 1 Cell, 3 Nature Genetics, 1 Nature, 2 PNAS and other excellent journals such as JCI and PNAS. Most of the papers are published with a member of the team as first or last author.

As stated above, the team not only includes the PI’s own group at the Pasteur Institute, but also a clinical group at the Trousseau Hospital in Paris and an electrophysiology group in Bordeaux, who investigates hair cell physiology and synaptic transmission. Both collaborations are very important to the overall success of the team. The three groups that constitute the Inserm 587 unit have regular meetings and, given the outstanding output, the management appears to be performed in an excellent manner.

The work is highly relevant, original and is clearly outstanding.

Assessment of the research team’s integration into its environment:

The team, which is the largest of the Neuroscience Department, appears to be well integrated into this Department, where it is certainly one of the most visible ones and contributes to its reputation. Interactions appear particularly strong with E2 whose focus is also on human inherited disorders. This interaction may be strengthened further in the future as the group leader intends to expand her research into the processing of auditory information in the CNS, where she may profit from the expertise in neuronal circuits and relevant techniques present in other groups. Her work is highly relevant for society because of its medical importance. The PI has been involved not only in organizing and co-organizing scientific symposia of high visibility (like the Titisee Conference on Sensorial Biology), but also in disseminating science to a more general public, in part through her activities at the Collège de France. The PI was the coordinator of an FP6 program of the EU (Eurohear), which brought together more than 25 European groups working in hearing and deafness. Very recently, she obtained an ERC Advanced Grant, which not only gives her rather flexible and generous funding over the next five years, but is also a distinction. Disregarding the ERC grant, which is just starting, her external funding has been excellent in the reporting period with a total amount between 2006-2011 of more than 5 M Euro.

Assessment of the research team's reputation and drawing power:

The reputation of the PI is outstanding, which is not only evident from the number of invited talks at international meetings, the (co)organization of international meetings, but also by the large number of very prestigious international prizes. Suffice it to say that she was awarded the very prestigious Prix Louis Jeantet de Médecine (2006), the Grand Prix Inserm de la recherche médicale (2007), the Pasarow Medical Research Award "Neuropsychiatry" - USA (2011), and most recently the highly prestigious Brain Prize of the Lundbeck Foundation (2012). In 2009, she gave the Alfred Fessard lecture at the French Neuroscience meeting, which recognized the best neuroscientists working in France. But also members of her team received prizes, one of the staff scientists was awarded the Jean Valade Prize of the Fondation de France (2005). In addition to the PI, who is invited to many international conferences, also members of her team regularly present at international meetings. She has established a large number of successful international collaborations.

This team has been attracting international postdocs and scientists. A case in point is the sabbatical in her team of a leading expert in sensory hair cell physiology from UCL (London), who had obtained the Chaire Internationale de Recherche Blaise Pascal to work in her group (2008-2009).

Assessment of the strategy and 5-year project:

Over the past ten to fifteen years, the team leader has successfully enlarged the scope of her research not only to include human genetics, but also an in-depth analysis of the proteins and functional networks involved in hearing and deafness. In the planned excellent projects, she extends her scope even more by expanding further into vision (a natural choice as Usher syndrome affects vision and hearing, and as several mechanisms appear to be similar) and into the information processing in the central nervous system, a move that the committee of experts considers important and promising. The group leader obviously will also continue her very successful work in understanding in detail hair cell physiology, including the molecules involved in mechanosensation and in synaptic transmission. In a final push to identify the remaining, so far unknown genes involved in human deafness she will make use of whole exome sequencing techniques that became available over the past few years (for limitations and needs see below). These projects are outstanding and promise to yield very important novel results.

A senior scientist of her laboratory will form his own group within the team that will focus on the parallels between hearing and vision, focusing at first on Usher genes as well as other genes identified in hearing disorders. Indeed, photoreceptors and sensory hair cells not only share e.g. ribbon synapses, but also ciliary processes, and fascinating data in this respect have been presented during the evaluation. Using various techniques, he intends to identify interaction partners of proteins involved in Usher syndrome, among others, and investigate their function using e.g. a Xenopus model system. Given both the high quality and importance of these projects, as well as the very good track record of this scientist, the committee of experts strongly supports him becoming more visible and directing a small group within the team.

Conclusion:

The team is clearly outstanding and its work of highest quality and visibility. The projects are outstanding and promising and will break new grounds. The committee of experts clearly supports that senior scientists gain more visibility and independence by forming somewhat more independent own groups within E1- this will be very important for their medium- to longer-term professional perspectives.

A certain current limitation is the fact that this team had to resort to external companies for whole exome sequencing and data analysis for their identification of novel human mutations underlying hearing loss. The committee of experts supports the wish to expand these techniques at the Pasteur Institute and preferably within the department, including the essential bioinformatics analysis of the data. Several other groups (e.g. E2 and E4) in the Department have essentially the same need.

The committee of experts recommends that this outstanding team goes ahead as planned.

Team 2: Human genetics and cognitive functions

Team leader: Mr Thomas BOURGERON

Workforce

Workforce	Number on 06/30/2011	Number on 01/01/2013	2013-2017 Number of producers**
N1: Professors or assistant professors	2	2	2
N2: EPST or EPIC researchers	2	2	2
N3: Other professors and researchers	1	1	1
N4: Engineers, technicians and administrative staff *on a permanent position	4	4	
N5: Engineers, technicians and administrative staff * on a non-permanent position			
N6: Postdoctoral students having spent at least 12 months in the unit	1		
N7: Doctoral students	4		
N8: PhD defended			
N9: Number of Habilitations to Direct Research (HDR) defended			
N10: People habilitated to direct research or similar	2		
TOTAL N1 to N7	**14**	**9**	**5**

• Detailed assessments

Assessment of scientific quality and production:

The research carried out by this team is outstanding in all respects. Two seminal contributions originate from this work: 1) the identification of one synaptic pathway associated with autism (the NLGN-NRXN-SHANK pathway); 2) the identification of the first mutation in the melatonin pathway linking genes to the circadian abnormalities observed in autistic patients and in many non-autistic individuals. The team has then moved on to demonstrated using animal models how mutated genes dictate the synaptic dysfunctions underlying psychiatric disorders affecting social cognition, such as autism and schizophrenia. These discoveries resulted in publications in top journals, such as Nature, Nature Genetics, and Molecular Psychiatry. These discoveries have been ground-breaking in the field of autism genetics, the quality of publications in this last 5-year period is outstanding and the reputation of this team in the scientific community is top rank.

Assessment of the research team's integration into its environment:

This team is very well integrated within France and within Europe. Several collaborations are on-going within the Pasteur Institute and the Neuroscience Department itself. It has national collaborations with very high-profile clinicians, both in France and in Sweden, as well as with geneticists, neurobiologists, and many leaders in their fields. The success at obtaining external funding from national and international sources is quite impressive.

Assessment of the research team's reputation and drawing power:

This team has earned a very high reputation at the international level. Over the years, starting from a small group, knowledgeable and talented young researchers were recruited, including neurobiologists, geneticists, psychiatrists and ethologists. The group leader has established a team of 14 persons, all with very good or excellent profiles, which contributed to his work and will further contribute to other major achievements in science. His team members appear very diverse in competence and past experience: while some would view this as a lack of focus, this diversity can be expected to foster an exchange of ideas and to further boost creativity and productivity. This aspect is instrumental to the science produced by this team, which bridges genetics with basic and clinical research, requiring integrated approaches and a diverse panel of expertise.

The PI is Director of the Neuroscience Department at the Institut Pasteur, member of the European Molecular Biology Organization, member of the scientific advisory board of the French Ministry of Health for research on autism. He is also Referee for the most outstanding scientific journals including Nature, Science, Cell, Nature Genetics, Human Molecular Genetics. He has received several honours and awards including the Vallery Radot award from the French Academy of Sciences, the Lacassagne award from the College de France and the Jean Bernard award of the Victories of Medicine in 2007.

Assessment of the strategy and 5-year project:

The team project for the next 5 years includes four tasks:

1.1) Genomic and clinical profiling of autistic patients using high-throughput SNP genotyping and whole exome sequencing;

1.2) Brain imaging and biochemical approaches to define endophenotypes in autism;

2.1) Cellular studies of the key synaptic molecules the team has identified as impaired in autism (NLGN, SHANK, CNTN) using human and mouse induced pluripotent stem cells (iPSC) to define and possibly reverse their abnormal phenotypes;

2.2) Developing and studying rodent model systems focused on the same molecules, by designing and applying new behavioural paradigms.

Within this framework, some specific tasks could require a more detailed definition of the experimental plan, while others may offer additional windows of opportunity to further strengthen the project. In particular:

(a) task 1.2 – The team seemingly wants to identify diagnostic biomarkers of autism remaining strictly focused on brain imaging parameters and on the serotonin-melatonin biochemical pathway. On one hand, it may be very complex to define genotype-phenotype correlations at the single gene level using brain imaging parameters; on another hand, this team has the power and potential to tackle (either on its own or collaboratively) the definition of biochemical markers of disease at a much broader level;

(b) task 2.1 – the structural and functional parameters to be assessed in iPSC studies should be defined in great detail. Furthermore, if the focus of this work will be mainly on fully-penetrant rare variants, then the task is fine. If instead the plan is to tackle rare variants which are not fully penetrant, the high-throughput chemical screening (HCS) used in a collaborative project may offer the opportunity to screen not only for chemicals able to revert synaptic, morphological and neurophysiological abnormalities in patient-derived iPSC cells, but also for environmental agents able to negatively impact neurodevelopment in genetically predisposed individuals;

(d) task 2.2 – the proposed rodent models represent an ideal setting to study the neuroendocrine, neurobiological and neuroanatomical bases of the skewed male-to-female (4:1) ratio generally present in autism and more specifically the relative protection of unaffected mothers transmitting to their male autistic offspring genetic/genomic abnormalities identified by this team (i.e., SHANK2).

Conclusion:

This team is characterized by an outstanding track record and has a challenging but promising project for these next five years. The project's strengths are multiple: (a) it is a logical follow-up of previous discoveries from the same team; (b) it has a high translational and heuristic potential, since it truly spans from the patient to basic science and back to the patient; (c) it uses excellent personnel and facilities; (d) it is linked to many French and European groups in constructive and productive collaborations; (e) it is extremely well financially supported. There is little doubt that this team will be successful at identifying new genetic pathways involved in human social cognition, at improving the diagnosis of autism spectrum disorder and possibly at opening new therapeutic avenues for this untreatable disease. The team is excellent in all respects and it well deserves to be granted during the next 5 years the maximum possible institutional support in terms of space, personnel, workload and core facilities (next generation sequencing and bioinformatics).

Team 3: Dynamic neuronal imaging

Team leader: Mr David DIGREGORIO

Workforce

Workforce	Number on 06/30/2011	Number on 01/01/2013	2013-2017 Number of producers**
N1: Professors or assistant professors	0	0	0
N2: EPST or EPIC researchers	1	2	2
N3: Other professors and researchers	0	0	0
N4: Engineers, technicians and administrative staff *on a permanent position	2 (IP FTE 100 %)	2 (IP FTE100 %)	
N5: Engineers, technicians and administrative staff * on a non-permanent position	0		
N6: Postdoctoral students having spent at least 12 months in the unit	3		
N7: Doctoral students	1		
N8: PhD defended	0		
N9: Number of Habilitations to Direct Research (HDR) defended	0		
N10: People habilitated to direct research or similar	0	0	
TOTAL N1 to N7	**7**	**4**	**2**

• Detailed assessments

Assessment of scientific quality and production:

This team has been established at the Pasteur Institute only in 2009 and therefore it might be a bit too early to judge its performance in the department. On the other hand, the PI already led a team at Paris Descartes from 2005 to 2009.

Using advanced optical tools, the team is performing excellent research, at the forefront of synaptic physiology studies. In the past five years the group leader has published a follow-up paper on his postdoc work at UCL (London, UK) dealing with the characterization of AMPA synaptic transmission at the cerebellar mossy fibre to granule cell synapse (Journal of Neuroscience). Two technical papers have arisen from the work of the team at its previous location (Université Paris Descartes). In the first one (Nature Methods), in collaboration with a team of physicists, it has been established that holographic methods can be used to shape the focal volume for photolysis of neurotransmitters in brain tissue. The second paper (Journal of Neuroscience) establishes a new combination of membrane dye/quencher (DiO-DPA) for optical imaging of membrane potential. This new combination, despite a few drawbacks linked to the capacitive effects of the quencher, offers one of the highest sensitivity to date and is being exploited and refined currently in the lab. Finally, a study of passive dendritic integration and dendritic filtering in cerebellar interneurons was recently published by a postdoc in the lab, as the first author, and the group leader as corresponding author in a top journal in the area of neurobiology (Neuron), demonstrating the power of the newly established techniques in answering relevant biological questions.

In the past, the team leader has had an excellent publication record with high quality publications (e.g.one publications as first author in Neuron), as well as publications in J Neuroscience (2 first author) during his Ph.D and postdoctoral period. The recent arrival in Pasteur does not allow estimating the long-term productivity (4 papers in the past 5 years) and impact but the publication of a research article in Neuron in 2012 combining optical techniques, electrophysiology and modelling is a good indicator that a strong research team is being built.

Assessment of the research team's integration into its environment:

The team leader is now coordinating the developments in optics for physiology in the Neuroscience department and is in charge of the multiphoton platform for physiology. He has obtained funding for these departmental equipments (NERF Ile-de-France Region 2010). The team has been funded by various agencies including ANR (as team member and coordinator). The consolidated 5 year external funding is in the order of 1.2 M€.

At the international level, the PI is the co-director of the Cold Spring Harbor Laboratories course on "Imaging structure and function in the CNS", one of the most attractive venue for young neuroscientists training. The team leader is member of the ENI-Net European network and of the Ecole de Neurosciences de Paris (a region funded body).

Assessment of the research team's reputation and drawing power:

The international reputation of the team is excellent, as demonstrated by the directorship of the team leader in a Cold Spring Harbor course. The team has attracted recently a talented permanent researcher and three foreign postdoctoral fellows. However there is only one PhD student in the group and no thesis was defended in the past 5 years. Renowned foreign researchers have spent a sabbatical in the lab or have been visiting scientists.

The team leader is invited to lecture for a number of international courses and meetings. The team maintains collaborations with 7 highly renowned international groups in Germany, Great Britain, Japan and the USA.

Assessment of the strategy and 5-year project:

The strategy of the Dynamic Neuronal Imaging team is positioned on the use of cutting edge optical techniques to study neuronal activity. In general, new technical developments were developed within the team before its inception at the Pasteur Institute (October 2009). The team has acquired 4 imaging setups (2 two photon, one confocal and a multipurpose spot and holographic setup). The arrival of a talented postdoc physicist coming from the lab of the inventor of STED, and who has been involved in many recent improvements in STED techniques, represents a major asset for the implementation of STED to monitor calcium transients and for other optical developments. After one year, he has already built a functional STED setup in the department. From this technical point of view human resources and funding are well adapted.

The biology projects proposed for the coming years are in general outstanding and promise to yield very important new information that can only be obtained with these top-notch optical techniques. The projects range from nanoresolution presynaptic calcium imaging to in vivo sensory information processing. Whereas the committee of experts expects that the first range of projects will be carried out with a high probability of success, the latter in vivo projects are beyond the current area of expertise of the team. This applies also to the proposed mathematical modelling, where some, but probably not entirely sufficient, expertise is present. Collaborations are under way. The proposed projects follow the current trends in cellular neurosciences, using techniques in part already developed in other leading laboratories, while adding new improvements. The acquisition of the necessary expertise in each field may take time. Attention should be put to develop a general strategy around a well-identified problem and to build synergies within the team. Furthermore, while the committee of experts very much appreciates that this team contributes a top-level imaging capability to the Neuroscience Department, the PI should be cautious not to spend too much of his time on the imaging platform but focus on well-defined biological problems and publication of high-quality papers. The recent Neuron paper from the group is already a very promising step in this direction.

Conclusion:

Overall, the Dynamic Neuronal Imaging team is a young and promising group, which is building a strong expertise in neurophotonics. It is clearly an asset for the Neuroscience Department. However, to optimize the scientific output at the team level, attention must be taken to build synergies between the different projects and focus on well-identified scientific questions. The arrival of a second permanent researcher and the presence of a technician will undoubtedly help building the stability and know-how necessary for new members of the team to fully exploit this rich environment and develop their skills. Consolidation of the international status and visibility of this team will ultimately depend on its publication output in the coming 5 years.

It is recommended to maintain the support and to allow for development of the STED technology in an adequate dedicated space and appropriate human resources.

Team 4: **Perception and memory**

Team leader: Mr Pierre-Marie LLEDO

Workforce

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers****
N1: Professors or assistant professors	1 (0.5 FTE)	1 (0.5 FTE)	1
N2: EPST or EPIC researchers	2	2	2
N3: Other professors and researchers	2	2	2
N4: Engineers, technicians and administrative staff *on a permanent position	3	2	
N5: Engineers, technicians and administrative staff * on a non-permanent position	1		
N6: Postdoctoral students having spent at least 12 months in the unit	4		
N7: Doctoral students	1 (0.5 FTE)		
N8: PhD defended	1		
N9: Number of Habilitations to Direct Research (HDR) defended	0		
N10: People habilitated to direct research or similar	2	2	
TOTAL N1 to N7	**14**	**7**	**5**

• Detailed assessments

Assessment of scientific quality and production:

This team investigates the cellular and molecular mechanisms of neurogenesis and the formation of neuronal circuits, using the olfactory bulb as model system (judicious choice as this structure is the only one in the CNS undergoing continuous neurons production throughout the whole structure in the adult). It addresses specific questions about the timing, reason and means of integration of new cells into existing olfactory circuits, and how they are affected in pathological conditions like some neurological and mental disorders. The topic is very exciting and has potential for high impact because it addresses a fundamental property of neuronal cells (the ability of some populations to renew themselves) that has remained poorly understood despite its importance for normal brain functions and diseases. Combination of state-of-the-art methods in cellular, molecular, behavioural and imaging methods, juiced up by the use of computational models. Translational to the clinic is notable and gives a new dimension to the work.

The group has established itself as a leader in the study of olfactory neuronal regeneration/renewal in post-embryonic mammals. They are well known for their work on olfactory bulb physiology in brain slices (including how the brain processes olfactory information) and on olfactory neurogenesis in the bulb and its precursors from other regions of the brain in neonates and adults. They have also studied how sensory processing is affected by experience and have recently been concentrating more on the "systems" end, including learning and memory. The rate of publication by the unit is excellent, as is the output quality. Since 2008 they have published 11 J Neuroscience and 2 Nature Neuroscience papers many of which make very important contributions. Overall the past record of production is outstanding.

Assessment of the research team's integration into its environment:

The team has several collaborations with other labs in the environment. Many collaborations with foreign labs exemplify a strong integration in the international community as well. Good valorisation of research through cooperative work with companies and training institutions (Medicen Paris Region), substantial involvement in public communication and society, patenting of new equipment (olfactometer), high and regular success in fund raising from various institutions and foundations. The team includes 3.5 permanent scientists apart from the PI. Significantly some group members have been authors (including last author) in papers that do not include the PI's name.

Although previously the team was very well funded, there seems to have been some decrease in this most recently with all but one grant ending by 2012, and the remaining significant one (ANR Blanc) ending 2013. This is a potentially very fundable topic using very modern methodologies and it would seem appropriate to seek other funding. A new award, "Laboratory of excellence" from French Research Ministry, was obtained for the period 2011-2020 corresponding to 520K€ - not a lot for 10 years but very prestigious.

The PI has been at the initiative of many successful applications for his team and for teams of the URA CNRS 2182 including the ENI-NET, Labex and ENP.

The team has been successful in attracting members with many different sources of funding and from different countries (5/13 members). 2 permanent scientists were recruited over the last 4 years. As a consequence, and because of the limitation in human resources imposed by Pasteur Institute, the number of PhD students decreased over the last few years. Interactions with other groups are very good even though they are restricted to the teams of the URA CNRS 2182.

Assessment of the research team's reputation and drawing power:

The group has very good reputation in the field of neurogenesis, and is acknowledged as one of the main players in neurogenesis in the olfactory system. There are several active collaborations within Pasteur, Paris, France, Europe and the rest of the world, many of which have led to very good publications that clearly show complementarities. National and international recognition is clearly demonstrated, including most recently membership of the Academia Europaea (2006), the Jaffe (2007) and Memain Pelletier (2012) awards from the French National Academy of Science, Camille Woringer Award (FRM), membership of the New York Academy of Sciences (2009), invited lectures all over the world, membership of editorial boards and refereeing for many bodies/journals, member of various scientific councils or advisory bodies, etc. – this includes having held the chair/presidency of several of these panels. All of this reveals clear recognition of scientific standing.

Assessment of the strategy and 5-year project:

The project emphasizes novel technologies applied to the olfactory bulb. Specific aspects include analyses of molecular and cellular processes necessary for the survival and functional integration of newly born neurons, the impact on morphological and functional maturation of synaptic contacts, the relevance for behaviour and psychiatric conditions (in line with the early model of bulbectomy and depression). The plan to extend their study to the hippocampus in addition to the bulb adds further potential to the model. The breadth of the projects reflects the integrative vision of the PI, and his drive to study neurogenesis from synaptic to behavioural level.

The plan involves extending the unit's previous work in a number of new directions, taking it into higher (more "systems") levels of organization and incorporating many new approaches and technologies. The group will extend its cell biological and physiological expertise to add optogenetic techniques combined with behavioural analysis in awake animals, long-term imaging in vivo and computational approaches. For some of these (e.g. optogenetic tools they have already demonstrated feasibility, e.g. by the recent Nature Neuroscience (2012) paper in which they stimulate OB neurons with light and shows that such activation facilitates learning and memory. Some of the other new areas (e.g. computational and translational aspects) are not disciplines in which the applicant has a significant track record and collaborations will be essential for their success. Overall the plan is ambitious and potentially interesting, but the breadth of the project may be excessive (at the expense of depth): the proposed projects lack experimental detail, as well as clear indications of how the novel techniques will address, and answer, specific important questions.

Conclusion:

This is an excellent group that has been producing world-leading work over the last period as a full unit (about 10 years) and proposes to continue to explore largely the same questions but incorporating a number of novel and modern approaches including optogenetic computational tools, as well as adding translational aspects. The proposal is disorganized, with work packages and questions not always relating to each other enough and questions not being clearly formulated. An effort should be made to structure better the different projects.

Despite these problems, the track record has been outstanding and the committee of experts expects continuity in scientific production and impact in the field for the next 4 years.

Team 5: Retrovirus and gene transfer

Team leader: Mr Jean Michel HEARD

Workforce

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers****
N1: Professors or assistant professors			
N2: EPST or EPIC researchers	3	3	3
N3: Other professors and researchers			
N4: Engineers, technicians and administrative staff *on a permanent position	3	2	
N5: Engineers, technicians and administrative staff * on a non-permanent position	2		
N6: Postdoctoral students having spent at least 12 months in the unit	1		
N7: Doctoral students	4		
N8: PhD defended	2		
N9: Number of Habilitations to Direct Research (HDR) defended	1		
N10: People habilitated to direct research or similar	2		
TOTAL N1 to N7	**13**	**5**	**3**

• Detailed assessments

Assessment of scientific quality and production:

The work performed by this team is based on hard-core basic science but with a highly translational, therapy-aimed target. The relevance, originality, quality and impact are clear. The team has performed work of major importance with real potential therapeutic avenues for patients with lethal neurodegenerative diseases. It has provided the proof of concept that AVV5-hNAGLU gene therapy is safe and efficient in dogs with mucopolysaccaridosis type IIIB (MPSIIIB) disease. All pre-clinical studies have been conducted to prepare a clinical trial: natural history of the disease, collection of patients, biomarkers of disease activity in the lysosomal storage diseases (LSDs) and pre-clinical efficacy, preparation of clinical batches, regulatory files. Other mechanistic studies have been conducted to elucidate the exact consequence of undigested saccharides on neurons functions

This work is very time consuming, extremely important because it allows translation between animal studies to human, but is poorly gratified in term of publications: 15 papers among which Plos One, Am J Pathol (IF 6), Mol Therapy (IF 6.8), Human Mol Genetics (IF 8), Stem Cells. However, only one member of the team is often author of the papers and the quantity of publications remain limited taking into account the size of the team.

Assessment of the research team's integration into its environment:

Several grants (865 k€) were obtained over the last 5 years. The team is also part of the LabEx REVIVE. The team leader has been able to secure all necessary funding, support and expertise to set up a clinical study using gene therapy. The funding for the iPSc project on amyotropic lateral sclerosis (ALS), however, has not been secured yet.

Interactions with other teams of the department are very limited and should be improved.

Assessment of the research team's reputation and drawing power:

The PI is a leader in the field of gene therapy of pediatric neurodegenerative disorders of childhood. He has coordinated between 2003 and 2011 the European consortium on Gene Therapy in paediatric neurodegenerative diseases. His group has validated a procedure for large-scale manufacturing of the AAV5-hNAGLU vector in insect cells, which has led to two separate phase I/II clinical trials on MPSIIIA and MPSIIIB, sponsored by the company Lysogene and Pasteur, respectively. Collaborations with foreign laboratories are seemingly active.

Whereas the international recognition of the PI in the field of gene therapy is certain with more than 20 invitations to national and international meetings, the visibility and recognition of the other members of the team, however, remains to be improved.

Assessment of the strategy and 5-year project:

The team leader is part time involved in the direction of the ANR. He will still direct a smaller team before he retires. The project has two parts. The first part concerns gene therapy in patients with San Fillipo Syndrome and the molecular mechanisms involved in this disease. The gene therapy project will be carried out by clinicians but the mechanistic studies should be more developed and extended.

The 2nd part of the project is focused on the analysis of molecular mechanisms of genetic versus sporadic (90%) forms of ALS using motoneuron derived from iPSc from affected or control patients. This project misses strong preliminary data and appears fragile if only based on iPSc.

Conclusion:

The main outcomes from this team are likely to be applications rather than new knowledge. Therefore, the quality and importance of this work would critically depend on the success of these applied aspects, including (but not exclusively) on-going clinical trials.

The team has strong experience in lysosomal diseases and has shown its ability to translate pre-clinical data up to clinical therapeutic research. This is of great importance. The team should continue to focus on this subject with emphasis on the mechanistic aspects. The development of another research theme with the limited size of the team appears difficult and a therapeutic strategy that would be based only on tests made on iPSc cells is at very high risk. Finally, the future of the team when the PI will retire is not clear since no strong projects are emerging at this stage.

Team 6: Integrative neurobiology of cholinergic systems

Team leader: Mr Uwe MASKOS

Workforce

Workforce	Number on 06/30/2011	Number on 01/01/2013	2013-2017 Number of producers**
N1: Professors or assistant professors			
N2: EPST or EPIC researchers			
N3: Other professors and researchers	1	1	1
N4: Engineers, technicians and administrative staff *on a permanent position	1.25	2.5	
N5: Engineers, technicians and administrative staff * on a non-permanent position	2		
N6: Postdoctoral students having spent at least 12 months in the unit	3		
N7: Doctoral students	1		
N8: PhD defended	3		
N9: Number of Habilitations to Direct Research (HDR) defended	-		
N10: People habilitated to direct research or similar	1	1	
TOTAL N1 to N7	**8.25**	**3.5**	**1**

• Detailed assessments

Assessment of scientific quality and production:

Research performed by this team addresses the mechanisms by which nicotine exerts its effects on behaviour and physiology in mammals, and the cellular and signalling pathways associated with nicotinic receptors and the dopaminergic system. This research is highly relevant to the medical field, and is original in that it focuses on specific mechanisms of cholinergic transmission and nicotine addiction, with a direct link to human. The work is of high quality and combines innovative and state-of-the-art methods with original animal models, and studies in human. The results produced are of primary importance for the understanding of basic biological processes related to cholinergic transmission and addiction and for the clinic. The team has a reputation among the leaders in the field.

Productivity has been high in yield and quality: 47 papers published by members of the unit since 2007, in 26 of which a member of the unit is first or last author. However the committee notes that the PI himself is first, senior, corresponding author of only 4 of the 5 top papers selected, and only 6 in total of the refereed original (non-review) papers since 2007. Some of these are from the unit but do not include him, others have him as sole author. This reflects some aspects of team organization: the group had two major semi-independent researchers who ran projects somehow separately and signed papers as last author. The Project “Dissection of phenotypes relating to cortical function” does not appear to have been led directly by the PI. The lentivirus system seems to be mainly his innovation. The new genetic study in humans looks interesting. Other projects are a mixture of some coming from his former lab, some apparently led by a former senior member of the team (2007-2009), with contributions from the PI.

Two senior members have now left the team. The PI is now supervising PhD students and postdocs directly, has a more traditional team since 2 years, and therefore is expecting to be lead author in more papers in the future.

Assessment of the research team's integration into its environment:

Funding is excellent – the PI is a partner in several very major projects lasting 10 years, and worth several M€ overall, coordinator of 700K€ FP7 project (to 2014), pharmaceutical grant of 300K€ to 2015 and more. The networks alone provide good evidence of collaborations (mainly within Europe) but there are also other collaborations in place (e.g. with RIKEN, Japan). There are also active collaborations within the Pasteur Institute and he is not only deputy director of the department but also plays a particularly active role in seminar organisation, retreats and other departmental communication activities.

Research valorisation is excellent: connection to a start-up company selling components for live imaging in awake, behaving mice, and to a pharma company for nicotinic agents. The topic has immense potential for the clinic. The group has been highly successful in raising funds, and has multiple pending applications. The establishment and running of the lentiviral platform is an immense asset for the department and the institute.

Assessment of the research team's reputation and drawing power:

The group's reputation has capitalized on the recognition of his former prestigious head, from whose team this group originally emerged. There has been a high number of invitations to national and international congresses. Although the PI is still at a relatively early stage in his career he is starting to be awarded prizes, including the recent award of the Prix Duquesne. Participation in international committees and reviewing panels also provide evidence of recognition. All of the PI's students are foreigners and there are multiple international collaborations through EU programs (ITN People BrainTrain), Neurocypres and FP7 Nico-Gene.

Assessment of the strategy and 5-year project:

The aim of the new projects is to carry out a multi-level analysis using genetic, neuronal and behavioural mouse and rat models to determine the respective roles of α3*, α5* and ß4*-nAChR subtypes for which human polymorphisms point to a role in nicotine addiction. Genetic studies implicate these receptors in nicotine addiction in humans but they had been overlooked by previous studies. They propose a number of new approaches (added to their previous pharmacologically-based approach) including for example a transgenic rat model (generated using lentiviral injection of early embryo). An interesting strategy (with lentivirus+Cre recombinase) is also proposed to express a gene of interest in a particular brain pathway. Another new strategy is in vivo brain imaging in awake behaving animals, using a fibre optic implant. This also allows calcium imaging and a number of variations that look interesting. Proof of principle is provided for some of these techniques, which look promising. Other extensions/new directions are proposed including a study of Alzheimer's Aß peptide in cholinergic signalling. These new projects are likely to yield important data, in particular the extension to studies in humans.

The proposed team has the PI as the only senior researcher – this is different from before – given that the PI was not senior author in so many papers. The committee of experts considers that a modest increase in size (to 12 members) would be a strong positive signal for a project that is interesting, timely and innovative.

Conclusion:

The team is very strong in its field, and does research highly relevant to the clinic and to the pharmaceutical industry. The research topics make up a complete program using animal models, sophisticated molecular tools, and combined behavioural and imaging techniques. It has clear strengths in methodological development as was also the case in the past with the pioneering of viral approaches, which largely contributed to the success of the lab. The unit has performed extremely well in the past although when one separates the work of the unit leader from those of his former mentor and from that of some of the senior researchers formerly in the unit, the leadership and originality of the group leader contributions becomes more difficult to assess. The PI's main strong points based on the work of the unit to date seem to be mainly as a superbly skilled experimentalist - however the proposed project is outstanding and has enormous potential. It shows a very good balance between novel, original ideas [including new questions] with novel techniques and approaches, suggesting that he does indeed have potential to lead a unit into distinct and original directions that are also important both from the point of view of basic neurobiology and for medical applications. Establishment of a new unit, and modest size increase, are recommended for this programme to be implemented.

Team 7: **Channel-receptor G5**

Team leader: Mr Pierre-Jean CORRINGER

Workforce

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers****
N1: Professors or assistant professors	1	1	1
N2: EPST or EPIC researchers			
N3: Other professors and researchers	1	2	2
N4: Engineers, technicians and administrative staff *on a permanent position	2	1	
N5: Engineers, technicians and administrative staff * on a non-permanent position			
N6: Postdoctoral students having spent at least 12 months in the unit	2		
N7: Doctoral students	1		
N8: PhD defended	1		
N9: Number of Habilitations to Direct Research (HDR) defended	0		
N10: People habilitated to direct research or similar	2	3	
TOTAL N1 to N7	**7**	**4**	**3**

• Detailed assessments

Assessment of scientific quality and production:

The team leader is an established senior researcher. During the last 5 years, his team has obtained a standing international recognition of their work on the X-ray structure of pentameric ligand gated ion channels (pLGIC). These receptors are integral membrane proteins composed of 5 subunits. They are the targets of neurotransmitters including Ach, GABA, 5-HT, glycine and glutamate. Due to their widespread expression in the brain, these receptors play major roles in brain physiological functions. They have been shown to be implicated in several brain diseases including Parkinson and Alzheimer disease, in nicotine addiction and epilepsy. pLGIC are the targets of a wide range of drugs. For example, the GABA-R receptors are potentiated by benzodiazepines, barbiturates, ethanol, general anesthetics, neuroactive steroids.

To gain into the structure of these receptors and the mechanism of action of drugs acting at the nicotinic, the glycine and the serotonin 5HT-3 receptors, the group has based his work on the study of a bacterial homolog from a cyanobacteria that he has discovered in 2007 named GLIC. This homolog is simpler in structure compared to the eucaryotic homologs and is amenable to expression, purification in large quantities and to X-ray crystallization. Thus, the team has succeeded in solving the structure of this integral protein at 2.9 Ångström in an open conformation. They also constructed several GLIC mutated homologs and investigated their X-ray structure to identify several distinct conformations that likely contribute to the activation or desentization process.

Remarkably, they further used the bacterial homolog GlIC as a structural surrogate of eukaryotic pLGICs to demonstrate the presence of a common general anesthetic binding site in the upper part of the transmembrane domain behind the gate of the channel. They proposed that this site contribute to the allosteric modulation of general anesthetics at the GlIC receptor, providing the principles of the mechanism of action of anesthetics. This work also provides the basis for further developing positive or negative allosteric modulators of this class of brain receptors. They also constructed a functional prokaryotic-eucaryotic chimera from the extracellular domain of GLIC fused to the transmembrane domains of the human alpha1 glycine receptor and investigated the ion channel properties and its pharmacological regulation by anesthetics. These data provides strong evidences that GLIC and pLIGC share similar structure, thus opening the way for X-Ray crystallography of the human allosteric sites.

15 publications are listed from 2007-2012: 8 as first or last authors by a member of the group, 3 are reviews in Nat Rev Drug Discovery (2009), J Physiol (2010) and Neuropharmacology (2011). Notably, 5 papers (Nature in 2007, 2009, 2011, PNAS 2011 and Nat Struct Mol Biol 2012) have been published with the first and last author being from the group. A member of the group is also the first author of 2 other papers published in J Mol Biol and the PNAS in 2010. 4 collaboration studies are published in Neuroreport (2008), Anesth Analg (2010), the PNAS and Neuropsychopharmacology (2011).

In conclusion, the group is continuing to obtain success in solving the X-ray structure of relevant important brain receptors and their associated druggable allosteric sites. The level of the publication is outstanding with 3 major publications in Nature and 3 others in high impact factor journals. Therefore, the group is at the forefront of his research field.

Assessment of the research team's integration into its environment:

Valorisation of the research has already started with the development of a collaboration with organic chemists (Chatenay Malabry) and a research contract with a pharmaceutical company for identifying novel molecules targeted to ion channels.

Ability to obtain external financing has been quite successful: the group is funded by the European PF7 grant which integrates 20 European teams (Neurocypress, 500 kEuros, 2008-2012) and by an ANR for 2011-2014 (Nico-chimera, 109 kEuros). The group is also funded by the Pasteur Institute (50 kEuros/year, a technician and a three year postdoc). The team received also 80 kEuros from Institut de France (2008-2011) and 50 KEuros from the DIM "Neurosciences and Neurodegenerative Diseases" (2009). In the light of the impressive work achieved by the team, it is reasonable to think that more national and international grants will be secured during the next years.

Assessment of the research team's reputation and drawing power:

The PI got a Pasteur Vallery-Radot award in 2009 and together with a postdoc received a French Academy of Sciences award for their research activity in 2011.

The team leader has given 25 invited lectures in symposia from 2008 to February 2012.

The quality of science and funding has been instrumental in the last years to hire excellent postdocs (4) and a technician (1). The group attractiveness also lead to the recruitment of 2 young associate scientists (CR1, CNRS in 2008 and Pasteur, 2012) and to the presence of a visiting scientist from Canada (6 months).

The success of this team in the X-ray cristallization of ion channels is based on a long standing collaboration with a crystallographer team with whom the group is sharing a postdoc. The group has also developed collaborations with computer and modelling scientists. Active collaborations with Canada (Ottawa) with experts in protein-lipid interaction and with an organic chemist (Faculté de Chatenay Malabry) for the synthesis of active compounds targeted to nicotinic receptors have been achieved.

Within the Pasteur department of Neuroscience, active collaborations are on the way to identify novel molecules targeted to the nicotinic receptors

Assessment of the strategy and 5-year project:

After several years dedicated to the identification of the X-ray crystallization of a bacterial homolog of pLGIC, the team is now focusing more on the understanding of the eukaryotic receptor structures, their conformational transitions from active to inactive states, the mechanism of action of drugs acting at allosteric binding sites and on therapeutic approaches of brain diseases. The activity that builds the strength of the group is of major interest and of cutting knowledge.

The main goals are :

The X-ray structure of portions and full-length human pLGICs: Based on their unique expertise, they proposed to solve the structure of the α7nAchR, the α1GlyR and the 5-HT3AR. They will first solve the structure of the human α1GlyR since they have already shown that the fused transmembrane domain of α1GlyR to GLIC recapitulated the known pharmacology of the receptor. This strategy using chimeric receptors might be decisive for the successful production, purification and crystallography of these proteins.

The extension of the chimeric approach to the extracelluar domain of full-length human pLGICs will be developed. Getting the structure of several allosteric binding sites that reside in the extracellular domains of these receptors, notably for the benzodiazepine binding site will represent major breakthrough in the field.

The structure of the cytoplasmic domain and interaction with clustering/regulatory proteins will be investigated. Selected GLIC chimera carrying the cytoplasmic loop of these receptors will be crystallized alone or in complex with known interacting cytoplasmic protein. These experiments should unravel the trafficking and associated regulation of these receptors by their intracellular environment.

In a second set of experiments, the group will try to solve new conformations of pLGICs to explore the states occurring during the process of activation/inactivation. Remarkably, the project will explore the allosteric binding sites that reside at the level of the ECD and the TMD to identify novel ligands acting at these sites. It will imply the collaboration of organic chemists and the in silico screening and docking of chemical libraries or of selected ligands.

The majority of these projects are supported by internal and external funding. The group will have to get more funding during the next years for several of the mentioned projects such as the functional investigations of allosteric pLGIC binding sites.

Conclusion:

The project proposes to realize a major effort in determining the X-ray structure of pLGIC receptors and more particularly several human receptors and to identify novel therapeutic tools. The hypotheses and the plan experiments are strong. The project is ambitious since the proposal extends to several pLGIC receptors at the same time. However, in the view of the excellence of the group and the competition field, it seems justified.

It is anticipated that the development of novel chemical tools and more particularly positive or negative allosteric modulators of these receptors will take several years. Moreover, the team leader will have to develop novel collaborations with teams of organic chemists.

In summary, this team has generated outstanding research during the last 5 years and has modified our general understanding of the mechanism of action of drugs such as general anesthetics acting at brain receptors. The team is capable of continuing to solve the X-ray structure of several pLGICs, leading to the understanding not only of how these receptors are activated and inactivated but also to the characterization of several allosteric binding sites that might be of the highest importance for understanding drug actions.

The committee of experts recommends to increase the space allocated to the team and to regroup the unit in the same building and the same floor to favour optimal scientific management.

Team 8: **Signaling in neural physiopathology**

Team leader: Ms Sheila HARROCH

Workforce

Workforce	**Number** on 06/30/2011	**Number** on 01/01/2013	2013-2017 **Number of producers****
N1: Professors or assistant professors	1	1	1
N2: EPST or EPIC researchers	0	0	0
N3: Other professors and researchers	0	0	0
N4: Engineers, technicians and administrative staff *on a permanent position	0	0	
N5: Engineers, technicians and administrative staff * on a non-permanent position	0		
N6: Postdoctoral students having spent at least 12 months in the unit	0		
N7: Doctoral students	0		
N8: PhD defended	1		
N9: Number of Habilitations to Direct Research (HDR) defended	0		
N10: People habilitated to direct research or similar	1	1	
TOTAL N1 to N7	**1**	**1**	**1**

- ## Detailed assessments

Assessment of scientific quality and production:

This team is young and in the growing phase. The team leader installed her independent unit in 2008 although she is still attached administratively to another unit (E4 and now E6). The team leader appears eager to set up a working group producing high quality science.The team has had 2PhD students (2008, 2010) and one Master student. During these few years she importantly contributed to a publication published in PNAS sharing co-corresponding authorship. In this manuscript the crystal structure of PTPRZ was solved and her team showed that PTPRZ is a pro-myelinating factor acting through a cell adhesion molecule: contactin-1.

The team leader is building up her international visibility: since 2008 and gave 3 talks at international meetings and more than 10 seminars at international universities and institutions. The team leader is interested in dissemination of science. In the last three years she wrote two reviews and one book chapter.

11 publications are listed from 2007-2012: 1 PNAS (2011) and 1 FEBS (2012) papers signed by PhD students as first author and by the team leader in senior position. 9 papers signed from collaboration studies and signed by the team leader in second-last or middle position are reported (Bone, Neuroscience, J Cell Biol, Mol Psychiatry and FEBS (review) in 2008; Bone, PlosOne, 2011; FEBS, J Immunology, 2012). The team leader has also patented data from her work through 2 patents (2008).

In conclusion, the group has identified potential novel roles of PTPs in oligodendrogenesis that might be therapeutically relevant. Thus it appears that the major work of the team is published in a high impact factor journal (PNAS) and through collaborations in middle to good impact factor journals.

Assessment of the research team's integration into its environment:

The team leader appears to be a very collaborative scientist, more than 10 international collaborations and 4 within her department. Collaborations are essential for the science and productivity of this small team. Ten papers have been published in the last years through internal and external collaborations.

Valorisation of the research has led to 2 patents concerning a new biomarker for oligodendrocyte progenitors and on PTPRZ deficient mice that have been delivered in 2008. Pasteur Institute has abandoned these patents in 2010.

Ability to obtain external financing has been limited to funding from an European Consortium dedicated to analyse the function, the structure and the regulation of PTP (250 Keuros for 4 years) during the period of 2008-2011. The recurrent support was around 20-26 Keuros/year. The team leader has obtained an ARSEP grant for 2012-2013 (20 kEuros).

Despite several intra-departmental collaborations, this team appears to be quite isolated. This might be due in part to the fact that it is located in a different building than the others.

Assessment of the research team's reputation and drawing power:

The team leader has been working since 2000 on oligodendrocytes and tyrosine phosphatase receptors, consequently the team leader has the know-how to develop the project aiming at understanding neurological and psychiatric diseases associated with myelin dysfunction. Since her work has been mainly done in collaboration it becomes important to establish how autonomous the team leader will be with the projects that are proposed for the next five years.

Assessment of the strategy and 5-year project:

Cross-talk between developing oligodendrocytes and neurons is critical to guide their morphological and functional maturation. Indeed, myelin dysfunctions appear to be involved in several neurological and psychiatric disorders. This group focuses on the contribution of contactin adhesion molecules and tyrosine phosphatase receptors (affecting contacting functions). Both contactins and tyrosine phosphatase receptors have been linked to disorders such as Autistic Spectrum Disorders, bipolar disorder and schizophrenia.

Among the tyrosine phosphatase receptors, the team has focused on PTPRZ showing in the past that this phosphatase is implicated in re-myelination after an inflammatory demyelinating insult.

On one side the team aims at understanding the cellular and molecular events underlying such a dynamic interaction between neurons and oligodendrocytes, on the other side they hope to discover novel therapeutic targets for demyelinating diseases and neuropsychiatric disorders.

Four major goals are set for the next five years: 1) elucidating the role of PTPRZ isoforms signalling and function in the development and survival of oligodendrocyte precursor cells and oligodendrocytes; 2) determining the specific role of PTPRZ in non-inflammatory demyelinating lesions; 3) examining additional roles for neuronal PTPRZ by studying PTPR-/- mice at cellular and molecular level. The team has (in house) two very interesting mouse models: PTPRZ -/- that show seizures, hyperactivity and other features mimicking a possible schizophrenic phenotype and the PTPRG -/- that show lack of interest in novelty, possibly mimicking a phenotype possibly more associated to depression. 4) Identification of PTP-CNTNs complexes in neurons.

The projects will explore specific signalling pathways and use "omics" strategies that consequently will generate a long list of molecules/interactors that the team would need to validate. This team is planning to perform extensive cellular, biochemical and behavioural work that requires expertise, funding and personnel that is not available presently.

Conclusion:

Such a small group should be more focused. In the absence of clear funding, this project will have a hard time to be developed. As a consequence the team is still young and the risk is that without significant support it will not progress.

5 • Grading

Once the visits for the 2011-2012 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 four criteria defined by the AERES and was given along with an overall assessment.

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

Overall assessment of the Neurosciences Department :

Unité dont la production, le rayonnement et le projet sont excellents. L'organisation et l'animation sont très bonnes.

Grading table:

C1 Scientific quality and production.	C2 Reputation and drawing power, integration into the environment.	C3 Laboratory life and governance.	C4 Strategy and scientific project.
A+	A+	A	A+

Overall assessment of the **team 1** "Genetics and physiology of hearing" (BOURGERON-PETIT):

Excellente unité à tous points de vue.

Grading table:

C1 Scientific quality and production.	C2 Reputation and drawing power, integration into the environment.	C3 Laboratory life and governance.	C4 Strategy and scientific project.
A+	A+	A+	A+

Overall assessment of the **team 2** "Human genetics and cognitive functions" (BOURGERON-BOURGERON):

Excellente équipe à tous points de vue.

Grading table:

C1 Scientific quality and production.	C2 Reputation and drawing power, integration into the environment.	C3 Laboratory life and governance.	C4 Strategy and scientific project.
A+	A+	NN	A+

Overall assessment of the **team 3** "Dynamic neuronal imaging" (BOURGERON-DI GREGORIO):

Excellente équipe à tous points de vue.

Grading table:

C1 Scientific quality and production.	**C2** Reputation and drawing power, integration into the environment.	**C3** Laboratory life and governance.	**C4** Strategy and scientific project.
A+	A+	NN	A+

Overall assessment of the **team 4** "Perception and memory" (BOURGERON-LLEDO):

Excellente équipe à tous points de vue.

Grading table:

C1 Scientific quality and production.	**C2** Reputation and drawing power, integration into the environment.	**C3** Laboratory life and governance.	**C4** Strategy and scientific project.
A+	A+	NN	A+

Overall assessment of the **team 5** "Retrovirus and gene transfer" (BOURGERON-HEARD):

Équipe dont la production et le projet sont très bons. Le rayonnement est excellent.

Grading table:

C1 Scientific quality and production.	**C2** Reputation and drawing power, integration into the environment.	**C3** Laboratory life and governance.	**C4** Strategy and scientific project.
A	A+	NN	A

Overall assessment of the **team 6** "Integrative neurobiology of cholinergic systems" (BOURGERON-MASKOS):

Équipe dont la production est très bonne. Le rayonnement et le projet son excellents.

Grading table:

C1	C2	C3	C4
Scientific quality and production.	Reputation and drawing power, integration into the environment.	Laboratory life and governance.	Strategy and scientific project.
A	A+	NN	A+

Overall assessment of the **team 7** "Channel-receptor G5" (BERGERON-CORRINGER) :

Excellente équipe à tous points de vue.

Grading table:

C1	C2	C3	C4
Scientific quality and production.	Reputation and drawing power, integration into the environment.	Laboratory life and governance.	Strategy and scientific project.
A+	A+	NN	A+

Overall assessment of the **team 8** "Signaling in neural physiopathology" (BERGERON-HARROCH):

Équipe dont la production et le rayonnement sont très bons. Le projet est bon mais pourrait être amélioré.

Grading table:

C1	C2	C3	C4
Scientific quality and production.	Reputation and drawing power, integration into the environment.	Laboratory life and governance.	Strategy and scientific project.
A	A	NN	B

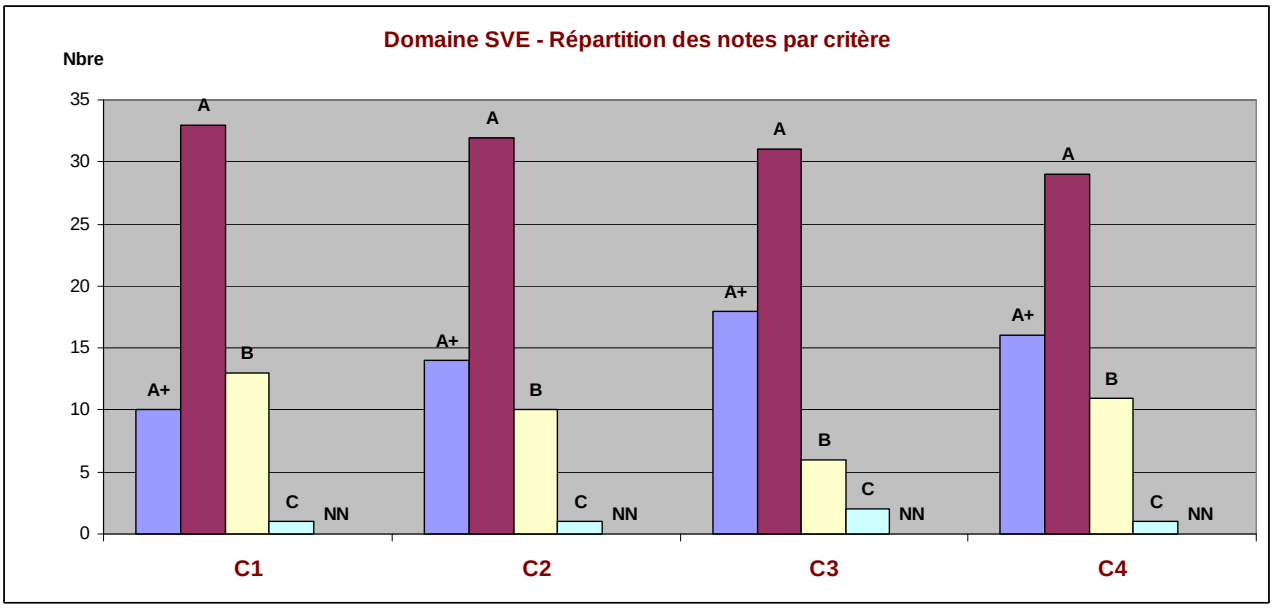
6 • Statistics per field

Notes

Critères	C1	C2	C3	C4
	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Gouvernance et vie du laboratoire	Stratégie et projet scientifique
A+	10	14	18	16
A	33	32	31	29
B	13	10	6	11
C	1	1	2	1
Non noté	-	-	-	-

Pourcentages

Critères	C1	C2	C3	C4
	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Gouvernance et vie du laboratoire	Stratégie et projet scientifique
A+	18%	25%	32%	28%
A	58%	56%	54%	51%
B	23%	18%	11%	19%
C	2%	2%	4%	2%
Non noté	-	-	-	-



7 • Supervising bodies' general comments

Dept

Human Genetics and Cognitive Functions Unit
Thomas Bourgeron
Institut Pasteur
25, rue du docteur Roux 75015, Paris, France
thomasb@pasteur.fr

Paris, 14 June 2012

OBSERVATIONS: No comment

Prof. Thomas Bourgeron
Director of the Neuroscience department of the Institut Pasteur
Director of the unit “Human Genetics and Cognitive Functions”
Professor at University Paris Diderot

Institut Pasteur

25 rue du Dr Roux, F-75724 Paris Cedex 15

Unité de Génétique et Physiologie de l'Audition
INSERM UMRS 587

Tel: 33 (0)1 45 68 88 90
<christine.petit@pasteur.fr>

Christine PETIT
Professeure au Collège de France

Paris, 13-6-2012

E1

OBSERVATIONS : No comment.

Christine PETIT

E2

Human Genetics and Cognitive Functions Unit
Thomas Bourgeron
Institut Pasteur
25, rue du docteur Roux 75015, Paris, France
thomasb@pasteur.fr

Paris, 14 June 2012

OBSERVATIONS: No comment

Prof. Thomas Bourgeron
Director of the Neuroscience department of the Institut Pasteur
Director of the unit “Human Genetics and Cognitive Functions”
Professor at University Paris Diderot

E4

Reply to the AERES report on the Department of Neuroscience at the Institut Pasteur

Project Leader: Pierre-Marie Lledo

(Note: Comments extracted from the AERES report appear in blue)

— June 2012 —

Because the report lacks clear sections (Strengths and opportunities; Weakness and threat; Recommendation), some statements appear rather ambiguous as they could fall easily in the category of "Strengths" as well as "Weakness". Therefore, we would like to take this opportunity to make some observations and clarifications that we hope will assist the reader as they read this report.

On page 20, it is stated: *"there seems to have been decrease in this most recently with all but one grant ending by 2012, and the remaining significant one (ANR Blanc) ending 2013. This is a potentially very fundable topic using very modern methodologies and it would seem appropriate to seek other funding."*

We would like to bring to the committee members' attention that **three** new ANR grants have been already secured for the **three** coming years and one Labex ("REVIVE") for ten years. In addition, we are actively securing funding for the coming years, and already have two additional grants under review (ERA-NET and ERC Advanced grant).

On page 21, we read: *"The breadth of the projects reflects the integrative vision of the PI, and his drive to study neurogenesis from synaptic to behavioral level".* And few lines later (page 21): *"Overall the plan is ambitious and potentially interesting, but the breadth of the project may be excessive (at the expense of depth)."*

Since the inception of the unit (2002), we have always performed multi-scale research, from synaptic function to behavior. This strategy led us to publish (among others) 5 articles in "*Nat. Neuroscience"* and 1 in "*Neuron"* with a first or last author from the team, so every 18 months on average. Indeed, the quality of our scientific production has been acknowledged by the committee (see *"the past record of production is outstanding"* on page 20). We seek to continue and even accelerate this pace of research without diminishing the breadth of our ambitions. To do this we will continue to use the most sophisticated techniques available, many of which integrate levels of description (e.g. optogenetics controlling behavior and electrophysiology, as in our most recent Nat. Neurosci. publication). We strongly believe that this strategy, which has been so fruitful in the past, will continue to reap benefits.

On page 20, "Assessment of the strategy and 5-year project", it is mentioned that: *"the other new areas (e.g. computational and translational aspects) are not disciplines in which the applicant has a significant track record and collaborations will be essential for their success".*

We would like to add context to this comment, as we believe it is inaccurate:

a) The P.I. has already published papers using theoretical approaches and appears as a leading author on two recent papers (J Neurophysiol. 2006 and Proc Natl Acad Sci USA. 2007). Also, as stated in our document, we have an ongoing collaboration with Nicolas Brunel since June 2011 (Expert in computational neuroscience; CNRS Paris) and we have recruited a mathematician as a post-doc in our lab (Martin Wierchert, since July 2011) to strengthen our expertise with this topic.

b) For the translational aspect, we are glad to read that *"Translational to the clinic is notable and gives a new dimension to the work"* (page 19). However, we disagree that we have no "*significant track record*". We would like to quote our recent translational papers that were mentioned in our report:
- Diaz et al., Bone marrow cell transplantation restores olfaction in the degenerated olfactory bulb. *J Neurosci* (2012) in press.
- Scotto-Lomassese *et al.* Fragile X mental retardation protein regulates new neuron differentiation in the adult olfactory bulb. *J Neurosci.* (2011) 31: 2205-15.
- Jaillard *et al*., Nxnl2 splicing results in dual functions in neuronal cell survival and maintenance of cell integrity. *Hum Mol Genet* (2012) 21: 2298-311.
- Tepavčević *et al.*, Inflammation-induced subventricular zone dysfunction leads to olfactory deficits in a targeted mouse model of multiple sclerosis. *J Clin Invest* (2011) 121: 4722-34.

We agree with the committee that proper collaborations are essential to successfully orient our activity to more translational goals. This is exactly why, over the past years, we have actively promoted close interactions with several experts in this field (among others, Prof. E. Corruble, INSERM U669, Psychiatric Department, Kremlin-Bicêtre Hospital; Prof. A. Gardier, Univ. de Pharmacie de Chatenay-Malabry and the members of a consortium call "Labex REVIVE" based on top-scientists on stem cells).

On top of page 21, it is stated: *"the proposed projects lack experimental detail, as well as clear indications of how the novel techniques will address, and answer, specific important questions."*

Because of space constraints, it is impossible to give sufficient detail on all of our projects. It is noteworthy that the fine details of all of these projects we proposed have already been evaluated by international referees and are supported by several ANR grants as well as ERA-NET or LABEX (known for their stringent peer-reviews). We believe that the continuous and long-term financial support of the Agence National de la Recherche testify of the coherence and the feasibility of the project.

E5

Institut Pasteur

Unité Rétrovirus et Transfert Génétique
INSERM U 622
Jean Michel HEARD

Paris, le 12 juin 2012

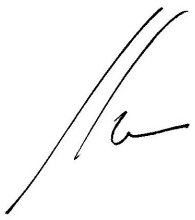
Monsieur Pierre Legrain
AERES

Objet: *commentaires*

Cher Pierre,

L'unité que je dirige a été créée par l'Institut Pasteur en 2000, puis par l'INSERM en 2004, avec des objectifs précisément décrits dans les dossiers de soumission qui ont été évalués par les commissions scientifiques respectives de ces deux institutions. J'ai considéré les décisions positives qui en ont résulté comme des contrats d'objectif. Je les ai remplis, et dans une certaine mesure dépassés, comme en témoignent les essais en cours de thérapie génique dans le cerveau de jeunes enfants atteints de maladie lysosomale, et d'investigation chez des patients atteints de sclérose latérale amyotrophique. L'absence de référence à ces objectifs atteints dans les commentaires du jury de l'AERES est d'autant plus inattendue que ces informations ont été délivrées avec soin lors de la présentation de mon unité. Les références négatives à des objectifs différents qui ne faisaient pas partie du contrat, et donc bien évidemment pas atteints, sont encore plus surprenantes. Il est regrettable que le concept de recherche sur projet, qui repose sur un contrat d'objectif, n'ait pas encore trouvé sa place à l'AERES.

Bien cordialement,



Jean Michel Heard

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Téléphone : +33 (0)1 45 68 82 46
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Email : jmheard@pasteur.fr

E6

Institut Pasteur

Neurobiologie intégrative des systèmes cholinergiques

CNRS URA 2182

Uwe Maskos, D.Phil.

Paris, le 13/06/12

I would like to thank the Committee for their time and effort, and after the correction of factual errors, do not have any comments to make.

Uwe Maskos

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http://www.pasteur.fr/recherche/unites/Nisc/home.html

E7

INSTITUT PASTEUR

Pierre-Jean Corringer, Research director DR1 CNRS

« Channel-Receptors » group CNRS URA 2182

I have NO COMMENT about putative personal observation of the AERES report concerning my research group.

Pierre-Jean Corringer
Le 12 june 2012

25-28, Rue du Docteur Roux
75724 Paris Cedex 15, France
Téléphone: 01 40 61 31 02
Fax: 01 45 68 88 36
Email : pjcorrin@pasteur.fr

E8

Department of Neuroscience
Sheila Harroch, PhD
Head of E3-Signaling in Neural Physiopathology
25 Rue du Dr Roux
75724 Paris, France
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Tel (33) 1 40 61 34 25

Paris, le 14 juin 2012

We thank the committee of the AERES for their positive evaluation and critique. As a result of this evaluation, and as recommended by the AERES, we are awaiting the support of the Institution to further develop our team and project. There are, however, a few points we do not feel were sufficiently addressed in this evaluation, and as it is difficult to fully grasp the situation within a limited time, we would like to comment on these points.

The resources of the team

It appears we were unclear regarding the different aspects of the resources (funding, expertise, and personnel) available to our team.

Funding: The funding we had during the evaluation period was of 80Keuros/year for one PhD student in the lab; the amount of funding raised is proportional to the number of personnel. The track record of the team leader shows her ability to raise independent external funding, having obtained an ATIP in 2004 (first of the neuroscience group), the first prize of the FRC in 2002, an ARC grant, the Pasteur-Weizmann honor, in addition to other funding since the time of her arrival at the IP. Most recently, the team was approached by a Russian startup company that proposed to fully cover the expenses of the lab (1 million euros) for the next 4-5 years. This funding is available.

Expertise: While the team itself indeed does not have very specialized expertise required for some aspects, it is readily available through already established collaboration with other teams. Furthermore, the vast majority of the cellular and biochemical approaches and techniques required for the project are the core skills of the team leader, and are already well-established in the team.

Personnel: The personnel are not presently available as historically, the team has been limited to a size of three. Three members are already in the team today. However, we expected with such funding to increase the size of the team to six members: A Canadian student currently in the lab will start a PhD and is part of the ENP PhD program, covering her salary for the duration of PhD studies; a researcher from China recently joined the lab in May, her salary is covered by a Chinese University; a Greek post-doctoral fellow has applied for various fellowships and would start in September; two other salaries (Israeli post-doctoral fellow and Russian researcher) will be covered by the Russian funding and are ready to join the lab in September (the various origins of the scientists recruited illustrates the international attractiveness of our group).

In consequence, t**he team will perform extensive cellular, biochemical and behavioural work with expertise, funding and personnel that are readily available.**

The autonomy of the Team

The autonomy of the team leader was questioned due to the number of collaborative works. However, we do not feel such a comment is appropriate. Most publications in top journals today are the result of different techniques and expertise, rarely found in one lab alone (for instance, a single lab rarely drives projects on both structural biology and phenotyping knockout mice), especially in one consisting of only three people. The team leader has raised her own funds and has published a paper with one PhD student in a top journal on a subject in which she is recognized to have expertise. She has presented orally three major projects, also submitted to high impact factor journals. **Her work thus far has been carried out in mainly collaboration due to limited human resources; however, the team has already strongly demonstrated its capacity to be completely autonomous in light of the techniques, skills, and resources present and available.**

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Tel (33)1 40 61 34 25

Paris, le 14 juin 2012

There are a number of facts that are not correct and comments that are misleading. In addition, the choice of words in English makes the meaning sometimes difficult to understand.

1. *«This team is planning to perform extensive cellular, biochemical and behavioural work that requires expertise, funding and personnel that is not available presently.* »
   In consequence, the sentence should be changed to **« The team will perform extensive cellular, biochemical and behavioural work with expertise, funding and personnel that are readily available »**

2. *Ability to obtain external financing has been limited to funding from an European Consortium dedicated to analyse the function, the structure and the regulation of PTP (250 Keuros for 4 years) during the period of 2008-2011. The recurrent support was around 20-26 Keuros/year.*

   The funding we had during this period was of 80Keuros/year for one PhD student in the lab; the amount of funding raised is proportional to the number of personnel. Thus there was no need to apply for more money. The track record of the team leader shows her ability to raise independent external funding, having obtained an ATIP in 2004 (first of the neuroscience group), the first prize of the FRC in 2002, an ARC grant, the Pasteur-Weizmann honor, in addition to other funding since the time of her arrival at the IP. Most recently, the team was approached by a private company that proposed to fully cover the expenses of the lab for the next 4-5 years.
   The sentence should be changed to « **Ability to obtain external financing has been demonstrated throughout the career of the team leader at the Institut Pasteur. Most recently, she obtained funding from an European Consortium dedicated to analyzing the function, structure and regulation of PTPs (250 kEuros for 4 years) during the period of 2008-2011 ».**

3. *« Valorisation of the research has conducted to 2 patents concerning a new biomarker for oligodendrocyte progenitors and on PTPRZ deficient mice that have been delivered in 2008. Pasteur Institute has abandoned these patents in 2010."*
   Valorisation of the research has **led** to 2 patents concerning a new biomarker for oligodendrocyte progenitors and PTPRZ-deficient mice that have been delivered in

2008. Pasteur Institute abandoned these patents in 2010, **but they are continued by a Russian startup company**.

4. *« The team leader installed her independent unit in 2008 although she is still attached administratively to another unit (E4 and now E6). The team leader appears eager to set up a working group producing high quality science that consist now of 2PhD students and one Master student. »*
   The second sentence, as originally written, is not clear in its meaning.
   « The team leader installed her independent unit, **limited to two additional team members**, in 2008, although she is still attached administratively to another unit (E4 and now E6). The team leader appears eager to set up a working group producing high quality science. **The team thus far has had 2 PhD students (2008 and 2010) and one Masters student**. »

5. *« The team leader is building up her international visibility: since 2008 and gave 3 talks at international meetings and more than 10 seminars at international universities and institutions. The team leader is interested in dissemination of science: in the last three years and wrote two reviews and one book chapter. »*
   The team leader gave talks at international meetings every year and not 3 talks.
   The team leader is not simply interested in the dissemination of science, but rather is invited to write reviews on topics for which her expertise is recognized.
   It should be changed to : The team leader is building up her international visibility: since 2008 **she has given talks annually at international meetings** and over 10 seminars at various international universities and institutions. **In addition, over the last three years the team leader has been invited to write two reviews and one book chapter, demonstrating international recognition for her topic of research.** »

6. *« ...9 papers signed from collaboration studies and signed by the team leader in second or middle position are reported (Bone, Neuroscience, J Cell Biol, Mol Psychiatry and FEBS(review) in 2008; Bone, PlosOne, 2011; FEBS, J Immunology, 2012). »*
   In none of the papers do I appear in second position.
   It should be instead « …signed by the team leader in **second-last** or middle position… »

7. *« In conclusion, the group has identified potential novel roles of PTPs in oligodendrogenesis that might be therapeutically relevant. Thus it appears that the major work of the team is published in a high impact factor journal (PNAS) and through collaborations in middle to good impact factor journals. »*
   One of the journals listed, Molecular Psychiatry has an IF of 15.5. It is cited in the report elsewhere as a top journal and yet here, only achieves « good » status.
   To maintain standards, it should be instead: « It appears that the major work of the team is published in a high impact factor journal (PNAS) and, through collaborations, in middle to **top** journals »

8. *« The projects will use pull-down and "omics" strategies that consequently will generate a long list of molecules/interactors that the team would need to validate ».*
   We are not quite sure what is meant by pulldown strategies.
   It should be instead « The project will explore **specific signaling pathways** and use –omics strategies that consequently will generate a long list of molecules/interactors the team would need to validate. **However, rescue experiments using KO cells and soluble domain of PTPRZ will considerably reduce the number of genes to study.**

E8

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Paris, le 14 juin 2012

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Funding: The funding we had during the evaluation period was of 80Keuros/year for one PhD student in the lab; the amount of funding raised is proportional to the number of personnel. The track record of the team leader shows her ability to raise independent external funding, having obtained an ATIP in 2004 (first of the neuroscience group), the first prize of the FRC in 2002, an ARC grant, the Pasteur-Weizmann honor, in addition to other funding since the time of her arrival at the IP. Most recently, the team was approached by a Russian startup company that proposed to fully cover the expenses of the lab (1 million euros) for the next 4-5 years. This funding is available.

Expertise: While the team itself indeed does not have very specialized expertise required for some aspects, it is readily available through already established collaboration with other teams. Furthermore, the vast majority of the cellular and biochemical approaches and techniques required for the project are the core skills of the team leader, and are already well-established in the team.

Personnel: The personnel are not presently available as historically, the team has been limited to a size of three. Three members are already in the team today. However, we expected with such funding to increase the size of the team to six members: A Canadian student currently in the lab will start a PhD and is part of the ENP PhD program, covering her salary for the duration of PhD studies; a researcher from China recently joined the lab in May, her salary is covered by a Chinese University; a Greek post-doctoral fellow has applied for various fellowships and would start in September; two other salaries (Israeli post-doctoral fellow and Russian researcher) will be covered by the Russian funding and are ready to join the lab in September (the various origins of the scientists recruited illustrates the international attractiveness of our group).

In consequence, t**he team will perform extensive cellular, biochemical and behavioural work with expertise, funding and personnel that are readily available.**

The autonomy of the Team

The autonomy of the team leader was questioned due to the number of collaborative works. However, we do not feel such a comment is appropriate. Most publications in top journals today are the result of different techniques and expertise, rarely found in one lab alone (for instance, a single lab rarely drives projects on both structural biology and phenotyping knockout mice), especially in one consisting of only three people. The team leader has raised her own funds and has published a paper with one PhD student in a top journal on a subject in which she is recognized to have expertise. She has presented orally three major projects, also submitted to high impact factor journals. **Her work thus far has been carried out in mainly collaboration due to limited human resources; however, the team has already strongly demonstrated its capacity to be completely autonomous in light of the techniques, skills, and resources present and available.**

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