IGF - Institut de génomique fonctionnelle

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Institute of Functional Genomics

IGF

Under the supervision of the following institutions and research bodies:

Nouvelle Université de Montpellier

Centre National de la Recherche Scientifique - CNRS

Institut National de la Santé Et de la Recherche Médicale - INSERM

January 2014

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

Department for the evaluation of research units

On behalf of AERES, pursuant to the Decree of 3 november 2006[1]*,*

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

On behalf of the expert committee,

- Mr Marc PARMENTIER, chair of the committee

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

Evaluation report

This report is the result of the evaluation by the experts committee, the composition of which is specified below.
The assessments contained herein are the expression of an independent and collegial deliberation of the committee.

Unit name:	Institute of Functional Genomics
Unit acronym:	IGF
Label requested:	UMR
Present no.:	UMR
Name of Director (2013-2014):	Mr Jean-Philippe PIN
Name of Project Leader (2015-2019):	Mr Jean-Philippe PIN

Expert committee members

Chair: Mr Marc PARMENTIER, Université Libre de Bruxelles, Belgium

Experts:

Mr Thomas BRAUN, Max Planck Institute for Heart and Lung Research, Bad Nauheim, Germany

Mr Eero CASTREN, University of Helsinki, Finland

Ms Elisabetta CERBAI, University of Florence, Italy

Ms Annette DOLPHIN, University College London, United Kingdom

Mr Christian GIAUME, Collège de France

Mr Mike LUDWIG, University of Edimburgh, United Kingdom

Mr Pierre MAECHLER, University of Geneva, Switzerland

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

Mr Cahir O'KANE, University of Cambridge, United Kingdom

Mr Pierre PAOLETTI, École Normale Supérieure, Paris (representative of CSS INSERM)

Mr Olivier PEYRUCHAUD, INSERM, Lyon

Ms Geneviève ROUGON, Université Aix-Marseille

Mr François VALLETTE, Université de Nantes (representative of CoCNRS)

Scientific delegate representing the AERES:

Mr Jean-Antoine LEPESANT

Representatives of the unit's supervising institutions and bodies:

Mr Thierry GALLI, INSERM

Mr Bernard GODELLE, Université Montpellier 2

Ms Nathalie LERESCHE, CNRS

Mr Jacques MERCIER, Université Montpellier 1

1 • Introduction

History and geographical location of the unit

The Institute of Functional Genomics (Institut de Genomique Fonctionnelle, IGF) originates from the CCIPE (Centre CNRS-INSERM de Pharmacologie-Endocrinologie), that was created in 1982 and later split into CNRS and INSERM units. The IGF itself was created in 2005, by the fusion of two CNRS units (directed by Mr Joël BOCKAERT and Ms Francoise MOOS), one Inserm unit (directed by Mr Claude BARBERIS), a unit supported by the Ministry of Research and Higher Education (directed by Mr Fréderic HOLLANDE, located at the School of Pharmacy), and other teams located in the nearby Institute of Human Genetics (Institut de Genetique Humaine, IGH). The IGF is dedicated to a multidisciplinary approach of intercellular communication and signal transduction, including signaling and functional roles of neurotransmitter and hormone receptors, covering many disciplines, from pharmacology to animal physiology. The specific areas of interest include the nervous, cardiac and endocrine systems and cancer. Starting in the CCIPE, a major effort has been put in the development of technological platforms, providing the various teams with state-of-the-art technologies in genomics, proteomics, *in vivo* imaging, and medium throughput screening assays.

The institute is located North of Montpellier, on the campus Arnaud de Villeneuve, which also hosts the Institute of Human Genetics (IGH) and the Center for Structural Biology (CBS), and is close to several hospitals and the School of Medicine of the Université Montpellier. The other main sites dedicated to Biomedical research are all located in the relative vicinity. Altogether, the IGF is therefore located in a very strong scientic environment (Pôle BioSanté Rabelais headed by Mr Joël BOCKAERT, the former IGF director) that is favoring the development of common resources and collaborations between groups.

The IGF was located up to 2010 in the former CCIPE building. In 2010, a new building, planned before the creation of IGF, was finally open after several years of successive delays. This allowed the institute to reach geographical unity (6400m^2) , to provide more space to existing teams, to recruit a number of additional teams (from 16 to 24 teams presently) and to host or expand some of the facilities.

Management team

The IGF is a unique place to do research thanks to its democratic management and the excellence of its teams, including the managing and administrative one. Overall, the experts committee felt that the institute is very well managed. The IGF was directed by Jean-Philippe Pin since 2011. He is assisted by a vice-director (Mr Gilles GUILLON), who is taking care of infrastructures and common services, and a General Secretary (Ms Anne CHABANNES), recruited in 2010, is responsible for administration. A steering committee, comprising the management and the department heads is taking the major administrative and scientific decisions. An international scientific advisory board (SAB) composed of five top level scientists from Canada, Germany and United Kingdom, advises the management regarding creation of new teams and other strategic issues. Prior to the present application, the SAB was consulted for advice regarding the structure of the teams and unit as a whole. An internal Scientific Committee composed of all team leaders meets at least four times a year for discussing scientific issues. A Laboratory Council, consisting in 4 elected members from each category of personnel (respectively researchers and professors, engineers and technicians, and post-doctoral scientists and PhD students) and 6 members selected by the management, is consulted three times a year to discuss the organization of the Institute. The scientific strategy of the IGF has been clever and clear:

- (1) recruitment of new laboratory heads based essentially on the talent of the candidates;

- (2) development of potent technical platforms in order to provide the best support for the teams of the institute.

The proposed management team for the future is unchanged except the replacement of the deputy director by Mr Philippe LORY.

AERES nomenclature

SVE1 LS1, LS2, LS4, LS5, LS7, LS9

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	28	22
N2: Permanent researchers from Institutions and similar positions	62	64
N3: Other permanent staff (without research duties)	43	48
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	1	1
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	93	4
N6: Other contractual staff (without research duties)	4	2
TOTAL N1 to N6	**231**	**141**

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	32	
Theses defended	63	
Postdoctoral students having spent at least 12 months in the unit*	38	
Number of Research Supervisor Qualifications (HDR) taken	18	
Qualified research supervisors (with an HDR) or similar positions	42	60

2 • Overall assessment of the unit

The IGF has a long standing history of excellent science based on a molecular pharmacology approach. The overall quality of the scientific output has increased during the last 5 years, relative to the previous period, as a result of the policy established by the present management. It is a place where there is a true scientific collective life that makes the research very efficient and the institute attractive. It is presently composed of 24 excellent teams involved in neuroscience, cancer, endocrinology and cardiac physiology, all sharing a common interest in extracellular and intracellular signaling pathways, particularly those involving G protein-coupled receptors and ion channels. The Institute is located in a very strong scientific environment and benefits from an outstanding set of technological platforms. Genomics, proteomics, *in vivo* imaging, screening and new animal facilities are all located within the Institute and managed by IGF scientists. Overall, the IGF provides an excellent combination of basic science and

translational research in many areas, with strong links with hospitals and the industry. This has led to the identification of a number of molecules with therapeutic potential, widely used bioassays and diagnostic tools, and discovery of genetic causes of some human diseases. There was also an exceptional output in terms of patents, spin-off companies and contracts with pharmaceutical and biotechnology companies. The director has a very solid international reputation in his field, and is surrounded by a number of outstanding scientists. He was successful in driving the IGF for the last 5 years, perpetuating the previous excellence while rationalizing the organization and expanding the number of teams through competitive international recruitment of ambitious young scientists with high potential. The experts committee felt therefore that the Institute will likely continue during the next 5 years to generate excellent science and further increase its international visibility and attractiveness.

Strengths and opportunities related to the context

The IGF has a long standing history of excellent science, with in house expertise in most aspects of extracellular and intracellular signaling.

The scientific environment of the Institute is excellent, with the nearby Institutes IGH and CBS, university campus, hospitals, and other sites of the Pôle BioSanté Rabelais. This environment favors efficient scientific collaborations and the implementation of common resources (technical platforms, recruitment strategies, infrastructures for social activities…). The strong chemistry pole of Montpellier, which gave rise to a major site of Sanofi-Aventis, is an opportunity for the development of candidate therapeutic molecules. The fusion of Montpellier Universities I and II should facilitate interactions with teaching structures and the recruitment of students at different levels.

The IGF has access to an exceptional set of technological platforms and state of the art equipment. Six of these platforms (genomics, proteomics, *in vivo* imaging, screening, vectors and animal facility) are located in the IGF buildings and managed by IGF scientists. Four of these six facilities were recognized (and partly funded) by IBiSA. The animal facilities (mouse, zebrafish, *Drosophila*) were significantly expanded recently. All these platforms appear very efficient and accessible, and they greatly contribute to technological developments. The network of all technical platforms of the Montpellier area (BioCampus Montpellier) is managed by one of the IGF team leaders. Altogether, the privileged access to these technical platforms and the corresponding expertise constitute un unvaluable asset for all IGF projects.

The IGF teams have maintained a good balance between basic science and efficient translational approaches, a strategy strongly encouraged by the management. As a result, strong connections with pharmaceutical and biotech companies and with clinical research teams have been established and maintained. This constitutes an excellent basis for further development of translational research activities. The IGF has also demonstrated its ability to attract financial support, from governmental agencies, charities and the industry.

The IGF had to cope with significant problems during the last 5 years including delays and high costs associated with the construction of its new building. The building was operational from 2010 on, but the opening of the new animal facility was delayed up to early 2014. In parallel, the Institute had to replace the general secretary, and a number of key persons involved in the maintenance of infrastructures and administration. This difficult period is now over, and the management will be able to concentrate mostly onto the development of scientific activities.

Many IGF scientists have strong international visibility in their fields, which results in strong attractiveness of the Institute as a whole. A new structure allowing to organize meetings and other events (Genopolys), should increase further its visibility and attractiveness as well as foster its interactions with the local and more distant environment (clinicians, industry, university…).

As a result of an efficient recruitment campaign, the IGF now hosts a high proportion of young scientists in the most productive part of their career. The new building still allows the recruitment of new teams or the growth of existing ones. This is a unique opportunity to stimulate high risk/high gain programs.

The existence of a scientific advisory board, which is consulted for the monitoring of teams and in the context of major strategic decisions, such as the hiring of new groups and changes in institute organization, is very valuable. Its role should probably be increased further, as new rules regarding the distribution of recurrent funds will likely require an external advice.

Thanks to its present management, the IGF has a clear vision and global strategy for the future. There is a clear Institute spirit and a friendly atmosphere. The director and its team are very dynamically and efficiently pushing the teams towards better science and stronger interactions between them.

Weaknesses and threats related to the context

The experts committee did not identify major weaknesses. The most obvious threats are essentially due to external factors that affect French science in general. These threats were clearly identified by the director and a number of changes in the management of the Institute were proposed in order to cope with them as much as possible and limit their impact on the ambitious goals of the Institute.

The total support received from CNRS, INSERM and Montpellier Universities did not change much over the last 5 years, despite a significant increase in the number of teams, scientists and technicians/engineers, and the opening of a new building. Therefore, the percentage of resources allocated to infrastructure support has increased to 44 % of the recurrent budget and this percentage will still increase further with the opening of the new animal facility. In addition, completion of the new building and the new animal facility has also required to inject significant funds originating from the CNRS/INSERM/University dotations. As a consequence, the teams have received and will receive less funding for running their research projects and will depend more deeply on external grants in a context that is getting less favorable in France (decrease of ANR budget). Funding the structure at an adequate level for meeting its objectives will therefore be a major challenge for the IGF.

The IGF is also suffering from insufficient technical support, particularly for common structures, such as administration, informatics, and the platforms hosted by the IGF (animal facility among others). A number of technicians and engineers will also reach the age of retirement within the next 5 years, which might increase the problem if they are not replaced.

The excellent technical platforms constitute one of the main assets of the IGF. It will however be a permanent challenge to maintain these platforms competitive and up to date, by upgrading/maintenance of existing equipment and acquisition of new ones. The time spent by scientists in the management of platforms is also detrimental to the progress of their own research programs. This was particularly obvious for some teams that have seen their scientific production decline significantly in parallel to their involvement in platform management. Ideally, an appropriate staffing by dedicated personnel would limit the burden of platform management.

Despite the excellent environment and the international recognition of the IGF teams, the ability to recruit excellent post-doctoral fellows is hampered by the combination of European and French regulations, which limit practically the duration of post-doctoral positions to 3 or 4 years. This is felt by present post-docs (both foreign and French) as far too restrictive.

Despite its attractiveness and the large number of HDRs hosted by the IGF, the number of PhD students recruited to the Institute is well below the standards. The limited access to PhD students is due to the low number of fellowships available in the Montpellier area.

The IGF was up to now very successful in raising funds. However, there is a relatively low fraction of funding coming from EU programs, despite the strong involvement of IGF teams in applied research programs with industry. Particularly, there was no ERC grants obtained so far.

Recommendations

The experts committee strongly support the present director and managing team, as they have demonstrated their ability to develop further the previous research activities, centralize the administration of the previous departments into a more homogeneous structure and attract a significant number of new teams, researchers and engineers/technicians. This strategy should be pursued. However, some of the teams are rather small. It might therefore be wise not to expand further the number of independent teams in the Institute, but rather to consolidate or rejuvenate existing teams by new recruitments. Moreover, precise rules should be elaborated for the replacement of group leaders who leave as well as for the promotion of inside researchers as group leaders.

Collaboration between different IGF teams for solving major scientific issues faster and more efficiently should also be encouraged.

The initiative to create (small) start-up packages for new groups recruited to the IGF is excellent and should be pursued.

A most crucial need is the recruitment of a budget leader and the staffing of the new animal facilities (mouse and zebrafish).

The basis of funding of IGF should be increased, particularly by stimulating applications to ERC grants by young promising scientists and established ones with high profile. Participation to more applied EU programs should also be encouraged. The plan to create a European grant office common to the other Institutes of the campus (IGH, CBS) is certainly a good initiative in this direction.

The IGF should increase further its recruitment at the international level, both for PhD students and post-doctoral fellows. The use of English as the common language for scientific activities at all levels was an essential step to improve the integration of foreign scientists. Learning French is however felt by fellows as necessary for daily life, both within the laboratory and outside. Attractiveness towards foreign PhD students and post-doctoral fellows should be further increased by making life in the laboratory really bilingual and increasing the help provided for solving administrative issues both inside and outside the Institute.

With the new plans for resource allocation to the various teams, the role of the SAB should increase further by counseling the management team in its choices in order to back up decisions and avoid internal tensions that may arise, particularly if the overall funding of the Institute would become short for its ambitious goals.

3 • Detailed assessments

Assessment of scientific quality and outputs

The IGF is composed of 24 teams mostly active in extracellular and intracellular signaling, with a particular focus on G protein-coupled receptors and ion channels. The long standing background of solid molecular pharmacology is applied to a number of topics in neurosciences, endocrinology, cardiac physiology and (intestinal) tumorigenesis. The scientific output of most teams is excellent to outstanding, and a number of IGF PIs are among the leaders worldwide in their respective fields. A number of major achievements and breakthroughs have been reached by IGF teams in the fields of GPCRs (structure determination, functional consequences of dimerization, modulatory role of partner proteins), ion channels (regulation of sodium permeable leak channel, role of calcium channels in pain perception), genomics (network of imprinted genes, mapping of replication origins), endocrinology ("memory" of endocrine cell networks), cell biology (characterization of intestinal tuft cells), translational biology (association of mutations with various human genetic diseases, identification of new targets and potential therapeutic molecules for a number of human diseases).

In quantitative terms, the IGF teams have published 349 original articles in international peer-reviewed journals since 2008, among which 212 with team members as first/last authors, and 137 resulting from publications from collaborations with external groups. 135 of these original publications appeared in journals with impact factors > 7, including Lancet (2), Nature (3), Immunity (1), Nat Cell Biol (1), Nat Methods (2), J Clin Oncol (1), Nat Neurosci (7), Circulation (3), Nat Chem Biol (3), Neuron (1), Nat Struct Mol Biol (1), Gastroenterology (4), Genes Dev (2), PLOS Biol (2), J Cell Biol (3), Blood (1), Nat Protoc (1), PNAS (16), Curr Biol (1) and EMBO J (7). There were also 140 reviews articles and 23 book chapters published during the same period. Compared with the previous 5-year period, there was a slight decrease in the number of publications per researcher, but the average quality of publications was improved, with a mean impact factor of 7.1 (6.4 during the previous period) and a significant decrease of articles published in journals with IF < 4. Overal, the scientific output is therefore stronger, per scientist, during the past 5 years, than during the previous evaluation period.

Overall, there is a very good combination of basic science and translational research in the activity of IGF teams. Excellent interactions with clinicians and various companies led to applications in many different fields (candidate drugs, diagnostic tools, widely used bioassays). All teams have established a good network of scientific collaborations. The key role played by the technical platforms hosted by the IGF in the impressive scientific production of the unit should also be emphasized.

Assessment of the unit's academic reputation and appeal

Many of the IGF staff scientists, including most of the present team leaders, have acquired a solid international reputation. This is illustrated by the large number of invitations to national and international meetings (428 altogether). These include 8 invitations to Gordon conferences and 6 to Keystone meetings, which constitute the most selective events in the research fields covered by IGF. Team members were also invited to give 318 seminars in institutes and companies all over the world. They have also organized 11 international meetings, including 3 Gordon conferences and one Keystone symposium.

IGF members were invited to write reviews in top journals in their fields, including Physiol Rev, Annu Rev Pharmacol Toxicol, Pharmacol Rev, Nat Chem Biol, Trends Neurosci, Trends Pharmacol Sci or Trends Endocrinol Metab. Twelve IGF teams are involved in 2 Labex programs, (EpiGenMed and ICST (Ion Channel Science and Therapeutics). Teams participated to 3 EraNet EU programs, and other international collaborative programs were held with China, Australia, Maroc, Ireland Canada and the Czech Republic. IGF scientists participated to many selection and evaluation committee in France (AERES, ANR, INCa, GSO, INSERM, CNRS, Atip-Avenir, IBRO) and abroad. They act as reviewers for top journals and are members of committees in international organizations such as IUPHAR and scientific societies. Members of the Institute received a total of 24 national or international prizes.

The IGF has demonstrated increased attractiveness over the past 5 years, with the recruitment, through international calls, of 6 new team leaders (5 of which funded by ATIP-Avenir grants), bringing expertise into areas such as GPCR crystallography or the use of Zebrafish as model. There was also the recruitment of 13 other new researchers (6 CNRS, 7 INSERM), 5 new assistant professors, 10 new engineers and technicians. In addition, 12 researchers and 8 technicians joined the unit, coming from other laboratories. 85 post-doctoral fellows were attracted to IGF over the period, among which 25 to 30 % from abroad. About one third of PhD students were

recruited from abroad. The IGF also trained 51 foreign scientists, from master students to full professors, who spent several weeks to several months in the Institute.

A large number of grants have been obtained, for a yearly total of 5.87 million € in 2012. For the 5 year period, the funding obtained include 6 ATIP-Avenir, 67 grants from ANR, 50 from other governmental organisms, 82 from various foundations, but only 6 from the EU. This latter number is relatively little for the size of the unit and its scientific level. IGF team members should therefore be more active in EU applications, particularly to ERC. They could also play a more important role in the mounting of networks applying to EU funding, which would be amply justified by their reputation, established international collaborations across Europe and privileged contacts with industrial partners. However, the ever increasing administrative burden associated to the mounting of such networks and their subsequent management may discourage such initiatives in the absence of specific administrative help.

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

For the last 5 years, the IGF had an exceptional output in terms impact on the economic environment. IGF team members filed 27 patents during this period, 10 of which were shared with or licensed to companies. A Biotechnology company, created on the basis of IGF results, was managed by unit scientists for several years, before being bought by a large pharmaceutical company in 2013, with the aim of developing drugs for colon cancer. Two other companies will be created shortly on the basis of IGF patents, with the support of FIST and SATT.

Three collaborative networks involving industrial partners were funded by the Fonds Unique Interministeriel (FUI) and 70 contracts were made with industrial partners. IGF members are members of the Scientific advisory boards of 5 Biotech and Pharmaceutical companies. A long term collaboration was established with a company developing bioassays, which has resulted in the co-development of widely used bioassays utilizing fluorescent probes and energy transfer technologies. This partnership led to creation in 2009 of a Collaborative Laboratory CNRS-CisBio Bioassays ("IGF Bioassays") for the further development of cell-based assays.

Stronger links were also created during the period with clinician teams in the nearby hospital. A new team has integrated IGF, whose team leader is director of the local Center for Clinical Investigation, which will foster translational research programs in the future.

Different topics of the IGF research were covered by the national and international press, such as the memory of endocrine glands, the resolution of morphine receptor structure, the development of artificial pancreas, the generation of induced pluripotent stem cells (iPSC) from centenarians, and the molecular basis of anorexia and schizophrenia. There is also a strong involvement of the IGF in the yearly "Brain awareness week" and other events directed towards the public.

Assessment of the unit's organization and life

The IGF has evolved from a structure involving several departments with their own administration into a more homogeneous structure with a centralized administration. This new organization is much more rational, with three thematic axes and four transversal axes, each of which supported by specific scientific animations with the aim of favoring exchanges and collaborations. The unit has a clear set of common scientific objectives. There are very good interactions amongst IGF teams, as demonstrated by the fair amount of common publications (67 out of 349 publications involved at least two teams) and by publications between IGF teams and nearby institutes (IGH, CBS).

All IGF teams have access to state of the art facilities, that are part of the Montpellier network "Biocampus". Six out of 12 facilities are located within IGF, and Biocampus as a whole is managed by an IGF team leader. An internal store has been created where the most common consumables are made available to the whole Institute. This store is funded by setting apart 10 % of all external grants. The administrative staff is also common to all teams.

The unit has very dynamic policies for recruiting new team leaders with high potential, through international calls and the advise of an external SAB, for importing new technologies and new research themes, as well as for providing to young investigators the opportunity to develop their own program either as team leader or within a larger team. Calls for PhD students and post-doctoral fellows are also organized at the unit level, which is providing international visibility of the unit and is also increasing the level of recruitment.

Programs of seminars are organized at different levels (unit, axes, teams). There is an excellent program of seminars with external speakers (one per week on average). Weekly team meetings and more occasional journal clubs

are also organized. Additional scientific activities are organized that contribute to the strong identity of the unit. This includes a two days meeting (IGF colloquium), organized every two years on a topic of high relevance to IGF and gathering international leaders in the field, and a scientific retreat (IGF days) of the whole Institute (3 days) organized every two years, in which IGF teams and platforms present their main achievements. English was established as the common language in all laboratory meetings and seminars. This contributes to the attractiveness of the unit towards foreign students and post-docs.

The management structures of IGF involve representatives of all categories of personnel, and these structures meet several times a year. Some improvement might be made in the information channels by which all IGF members are informed of the decisions made by the management. The web site of the unit is informative and describes the general policy and goals of IGF and the specific research programs of all teams. Following the opening of the new IGF building and of the Genopolys building, the unit has all necessary premises for scientific and social activities.

Meeting with the ITAs (Technical staff) was informative and lively. They are working either on platforms or in research teams and all seem to be committed to delivering the best services to the scientists. They also seem to form a coherent group of people who are interacting easily with each other.

They raised several issues that are probably beyond the control of management. These included:

- the mandatory termination of contracts after 6 years employment, even when grant money is available. It is important to note that they do not necessarily feel entitled to permanent jobs;

- the limited options available for promotion despite the fact that last year a fair amount of them have been promoted by CNRS (not INSERM) compared to national ratios;

- difficulties for those working in "common services" to be kept informed of all major decisions;

- lack of personnel for administration (accountant) and mouse facility.

Overall, the experts committee feels that the ITAs are highly qualified and motivated.

Assessment of the unit's involvement in training through research

The number of professors and assistant professors hosted by IGF significantly increased over the past 5 years. They were 18 in 2009, presently there are 27 professors and assistant-professors among which several PU-PH (8). Five assistant-professors have been recruited. All of them have teaching and/or organizational responsibilities. IGF is affiliated to the CBS2 ED 168 doctoral school (Sciences Chimiques et Biologiques pour la Santé) for which both the director and deputy director are IGF members. IGF is affiliated to the master BIOMED, IGF members are deeply involved the organization and teaching of specific modules such as neurobiology, endocrinology, signaling, pharmacochemistry. IGF also recruits students from the masters Biotin (Functional genomics, food biohazards) and “Life engineering”. Many full time researchers of the institute are teaching in Universities Montpellier I and II, and in other doctoral schools (Paris, Strasbourg, Nimes, Lyon) and abroad (China, USA). In addition, they participate to many thesis defenses and students’ selection jurys.

IGF is strongly involved in training through research. Despite the limitation of PhD recruitment as a result of the paucity of PhD fellowships in the Montpellier area (only 18 fellowships for a total of 400 HDR within the CBS2 graduate school), 77 PhD theses were defended during the past 5 years. In parallel, 19 new HDR were obtained. The training output has shown a significant progression compared to the previous 5 year period (47 PhDs, 7 HDR). PhD and students recognize the high quality of the training (i.e. seminar programs) and supervision (comité de thèse), and the outstanding technological environment in which they are trained. IGF co-organized (2011) an IBRO (International Brain Organization) meeting for the Young Investigator visiting program (1000 participants) as well as an Electophysiology school and several technological training sessions on their technical facilities. The unit also hosted 61 master 1 and 94 master 2, in addition to licence students, BTS and IUT.

Assessment of the strategy and the five-year plan

Given the size of the IGF and the number of teams involved, the projects are obviously diverse and each team program is analyzed separately in the next section of the report. Nevertheless, the IGF is much more than the juxtaposition of individual teams and research programs. All teams have acknowledged the importance of the strong scientific environment of the Institute, of the outstanding technological resources provided (platforms) and of the

direct collaborations with other teams. Besides the specific model systems and molecules studied by each group, there is a true project of the unit as a whole, thanks to the very strong combination of teams with shared expertise and interests. The overall objective of the IGF for the next 5 years can be summarized as the functional and structural characterization of GPCRs and ion channels, of the protein complexes (signalosomes) containing them, and of the intracellular signaling pathways and cellular networks they regulate in the control of neuroendocrine systems, heart and oncogenesis. Major efforts will be put on the analysis of *in vivo* consequences of the main findings in animal models (mouse, zebrafish, *Drosophila*), thanks to the development of animal facilities, and on the introduction of new technologies (optogenetics, epigenetics). More emphasis will be given to bioinformatics and system biology, with the aim of recruiting new researchers bringing in their expertise in these areas. As in the recent past, translational research will aim at the identification of new therapeutic strategies and diagnostic tools for various neurological, psychiatric, endocrine, cardiovascular and oncological diseases.

Overall, this program is a strong association of fundamental, translational (collaboration with clinicians) and applied research (spin-off companies, patent-generating projects) and a good balance of risk-taking and feasibility. Many of the individual team projects are at the forefront of their respective fields and the ambitious goals are backed by the recent arrival in the unit of several new team leaders with high potential. The IGF teams have also an established network of excellent collaborations worldwide. Stronger links with the nearby hospital have been created with the arrival of one team essentially composed of clinicians and whose team leader is director of the local Center for Clinical Investigation. The IGF has also long term and strong links with pharmaceutical and biotechnology companies, and there is no doubt the fruitful interactions with these companies will be pursued in the future.

The present director has a very solid international reputation in his field and is surrounded by a number of other outstanding scientists. He was successful in driving the IGF for the last 5 years, perpetuating the previous excellence while expanding the number of teams by the competitive international recruitment of ambitious young scientist with high potential. The management team has a very clear vision of the strengths of the IGF and the factors that might limit its development in the future. A number of proposals have been introduced in the plan in order to adapt the IGF structure to its future challenges. Changes were made to the general organization, from 5 departments (neurobiology, molecular pharmacology, Physiology, Endocrinology, Oncology) into a more integrated structure with three thematic axes (Neurosciences, Physiology and Cancer biology) and four transversal axes (GPCR signaling, Biology of ion channels, Molecular and cellular networks, Translational biology). This new structure is expected to stimulate further interactions and collaborations between IGF teams and the experts committee support fully this view. The management will also stimulate the teams to collaborate more deeply with clinicians and with the private sector. In order to increase solidarity amongst IGF teams and anticipate potential grant shortage in the future, the institute plans to allocate its resources differently. Up to now, recurrent funds were distributed on a proportional basis among the teams. From now on, part of the recurrent funding will be used to support risky and ambitious projects not yet funded (or which failed to get funded) in order to drive them to a better position for securing further funding. The experts committee fully supports this proposal, that will provide more space for strategic decisions and a greater capacity to adapt to the changing environment.

Overall, the experts committee felt that the Institute will likely meet most of its ambitious goals, continue during the next 5 years to generate excellent science and increase further its international visibility.

4 • Team-by-team analysis

Team E01: Pathophysiology of Synaptic Transmission

Name of team leader: Mr Laurent FAGNI - Proposed new leader: Ms Julie PERROY

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	4	4
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	4	
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**9**	**5**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	1	
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	3	4

• Detailed assessments

Assessment of scientific quality and outputs

The team is internationally known for its work on the receptor complexes (receptorsomes) involving glutamate receptors. In particular, the team has been innovative in developing novel imaging techniques, including single-cell BRET and 2-photon fluorescence fluctuation microscopy. These original methodological developments have led to the

identification of several protein-protein interactions within glutamate receptosomes, such as PICK1, SHANK3 and Rich2. These findings were reported in 20 publications. In 10 of them, team members are the first or the last author, these include Nat Neuroscience, J Cell Biol, J Neurosc, Annual Rev PharmTox, and others. The high level of publication forum speaks for the high quality of the output. The former team leader is a highly respected and well-cited author in the field (h-index 37) and the new team leader is a young investigator rapidly gaining international recognition. The team has a dense network of cooperations within the institute and nationally, but international collaborations are relatively few, at least those that have led to joint publications.

As the current team leader has several national commitments and is also taking responsibility of the neuroscience axis of the IGF, a new team leader will take over the lead of the team. Although this transition is apparently taking place smoothly, it may have impacted the output of this evaluation period. It appears important that current and future team leader work in concert to maintain scientific excellence and leadership during this transition period.

Assessment of the team's academic reputation and appeal

The team is internationally recognized, which is evidenced by the number of invitations to international meetings and an invitation to write a chapter in the Annual Review of Pharmacology and Toxicology. Laboratory members receive invitations to act as *ad hoc* reviewers in the leading international journals. The laboratory continues to attract foreign postdoctoral fellows and visiting scientists of high quality. Laboratory members have a highly recognized status in scientific organizations, for example, the current team leader has been secretary general of the French Society for Neuroscience until 2011. The team is participating to the Labex EpiGenMed.

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

The team has a sequence of industrial contracts, now the main contract is with the 2 biotechnology companies, these also involve 2 patents with team members. Discussions are ongoing for the possible creation of a startup company. The team has been active in the Brain awareness week activities.

Assessment of the team's organization and life

The current team leader has been appointed to lead the Neuroscience Axis in the proposed new organization of the institute. One of the team members is a scientific manager of the animal facility, which is currently being expanded and reorganized. The team is logically organized around a coherent topic and has been very active in collaborations within the institute. The team is clearly benefiting from the research environment within the Pôle BioSanté Rabelais.

Assessment of the team's involvement in training through research

The team is involved in the management, evaluation and teaching of several master programs in the two Universities of Montpellier. A single PhD student and 5 master students graduated during the previous evaluation period, apparently one student left without achieving a PhD degree. Now, there are 3 graduate students and 5 postdoctoral fellows in the laboratory.

Assessment of the strategy and the five-year plan

The 5-year plan is a logical continuation of the research line followed in the team up to now, namely, the analysis of the protein networks within glutamatergic synapses using imaging methods, that are now proposed for the study in animal models of human diseases. The plan proposes 3 major projects, each of which is based on an approved national grant:

- trafficking, targeting and recycling of glutamate receptosomes and molecules involved in these processes: differential targeting of different mGluR types will be utilized to analyze the role of motor and scaffolding molecules in targeting and trafficking. BRET and FRET imaging will be utilized in cultured neurons;

- characterization of glutamate receptosomes in presynaptic terminals of thalamocortical network: this work is based on the Nature Neurosci publication from 2008. It is not clear whether the work will be performed *in vitro* or

in vivo, probably *in vitro*. The team will use optogenetics to differentiate between cortico-thalamic and thalamo cortical neurons and then study the synapses where mGlu7a/PICK1 interaction takes place. Use of optogenetics for the dissection and selective activation of particular neuronal types is feasible, but the plan does not specify how the individual cell types will be targeted. It also fails to elaborate on what exactly will be analyzed once the cell types have been identified;

- glutamate receptosome in dendritic spines. Three different culture types will be investigated, hippocampal, striatal and cerebellar Purkinje cell cultures. It is not clear whether all the studies will be conducted in cultured neurons or whether slices or *in vivo* models will also be employed. Interactions of mGluR5 and Homer will be compared in FraX and wildtype mice using BRET/3DSIM microscopy, which is a new technical development. Interactions of mGluR5 and D1 receptors will be investigated in cortico-striatal cocultures. mGlu1 and GluDelta2-interactions will be analyzed in Purkinje cells, based on preliminary observations that mGlu1 signaling gates GluDelta2 channels.

Overall this is a timely project with important objectives. However, the plan is heavily based on the application and further development of the imaging technology previously developed in the group. This makes the plan consistent and feasible, but may reduce innovativeness and risk-taking components. In particular, there are few plans to extend the findings to *in vivo* conditions, even though several disease models are proposed to be used. The use of animal models was relatively superficially described.

Conclusion

This is a strong and highly recognized team that has done excellent methodological developments and obtained groundbreaking data on receptosomes. Future developments and group leader transition should be carefully managed.

- **Strengths and opportunities:**

- high-quality scientific output with strong publication record and international visibility;

- clear niche in the field of glutamate receptosome;

- innovative development of new imaging techniques;

- availability of IGF and other core facilities;

- industrial contacts.

- **Weaknesses and threats:**

- leadership of the new team leader yet to be consolidated;

- mostly *in vitro* work, need to open towards *in vivo*;

- diverse plan, need for focusing;

- few new openings in the 5 year plan.

- **Recommendations:**

The team is now in transition to be led in the future by a new leader. She is taking the leadership of a large team with relatively diverse interests. This transition should be scrutinized and supported by the Institute. The experts committee recommended that the team focuses more on the core competence of the new team leader. The development of imaging techniques towards slice or live animal applications would be advisable to make the disease models more convincing. The team should strive to be successful in European grant programs, such as ERC and Horizon 2020.

Team E02: Neuro-glio-vascular interactions

Name of team leader: Ms Mireille LERNER-NATOLI – proposed new leader: Mr Nicola MARCHI

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	2 (0,50)	2 (0,50)
N2: Permanent EPST or EPIC researchers and similar positions	2	2
N3: Other permanent staff (without research duties)	2	2
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**6 (4,5)**	**6 (4,5)**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students		
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	2	2

• Detailed assessments

Assessment of scientific quality and outputs

During the evaluated period, the research of the team was focused on Blood Brain Barrier (BBB) damage and clinical drug resistant epilepsy. In 2013, a young researcher has been recruited at the CNRS (CR1) and is proposed to be the new leader of the team, the present leader being unable to carry on for medical reasons. His background and interests are overlapping with those of the former team as, during his long stay in the US, he has worked in the field of epilepsy with a particular interest in the role of BBB damage in epilepsy and the role of BBB drug transporter and metabolic enzymes in drug resistance.

The scientific production during the five past years is 32 scientific papers in peer-reviewed journals with an averaged impact factor ranging from 2 to 5. The list however includes 5 papers in journal with higher ranking (Nature Neuroscience (1), Journal of Neuroscience (2); Neurobiology of Disease (1); Journal of Cerebral Blood Flow and Metabolism (1). The members of the team have also published 10 reviews, including one in Brain (IF 10) and the Neuroscientist (IF 6). This publication track illustrates the regularity of the production of the team in journals of good level. Moreover, the current and future team leaders have participated to 10 national and international meetings as invited speakers indicating the good visibility of the work performed by this group in the field of the Blood Brain Barrier and epilepsy. Finally, it should be noted that the two team leaders are co-authors of a review in the Neuroscientist published in 2013 focused on cerebrovascular remodeling and epilepsy.

Assessment of the team's academic reputation and appeal

The former team leader has received 10 invitations at International and National meetings and has been Chairman of a Symposium at the Colloque de la Société Française des Neurosciences (Marseille, 2011). Another member of the team has received 12 invitations at national and international meetings. Finally, the proposed new team leader has been in charge of several administrative and clinical responsibilities in the US. However, only one postdoctoral fellow (French) has been hosted by the team during the evaluated period.

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

In addition to specialized publications, team members have been involved in different actions promoting science. One member is in charge of the “Réseau Sentinelle National - Mortalité dans l' Epilepsie”. A clinical book has been recently published: “Le syndrome de Lennox-Gastaut” by Drs. Gelisse and Crespel (John Libbey Eurotext, 2010). A book chapter was also published: “Therapeutic targets and perspectives in the pharmacological treatment of epilepsy”, UNI-MED Verlag Ed. 2011. Clinic, USA (Dept. of Neurosurgery). In 2012, the former team leader was nominated member of the European Dana Alliance for the Brain (EDAB) after she organized the "Brain Awareness Week" in Montpellier.

In addition, the laboratory has developed partnership with several hospitals (contracts - Clinical Project CIC and CHRU: “Marqueurs de rupture BHE dans l’ELT”). The team has access to human biological samples and this translational research effort is based on a network of collaborators, including the Centre Hospitalier Universitaire (CHU) in Montpellier, the CHU in Nimes (Epilepsy unit), the Hôpital de la Timone in Marseille (Neurophysiologie) and the Cleveland Clinic, USA (Dept. of Neurosurgery).

Finally, the team has obtained grants with a pharmaceutical company. Title: effets d’une molecule “pro-Ang1” sure la perméabilité de la BHE et sur l’épileptogenèse *in vivo*.

Assessment of the team's involvement in training through research

Most of the permanent researchers of the team are involved in teaching duties: at Master level, M1, UE « Modèles animaux, mécanismes physio-pathologiques en neurologie »; M2, UE « Processus de communication et d'intégration dans le système nerveux central »; Diplôme Inter-Universitaire (DIU) d’Épileptologie. They are also involved in the organization of the DIU « Épileptologie, formation des médecins étrangers ». Another team member is the person in charge of the Formation à la recherche Clinique, DIU « Épileptologie ».

During the evaluated period, the members of the team have trained 5 licence students, 2 Master 1 and 2 Master 2 students. 4 graduate students defended their thesis. The proposed new team leader has in the past years directly managed one research technician and two post-doctoral fellows. Importantly, since his arrival at the IGF, the new team leader has started to interact with the personnel, organizing laboratory meetings, assuring the progression of the research. He has an experience on research involving collaboration with doctors and with the use of patients’ specimens as he was responsible for the maintenance and revision of human research protocols.

Assessment of the strategy and the five-year plan

The 5-year project of the team is based on the background work of both the current and the future new team leaders and their published data. It is a research project focused on a multi-modal experimental approach that plans to use rodent models of seizure, a model of malformation of cortical development, an *in vitro* model of BBB, and an

electroencephalographic analysis of organotypic hippocampal slice cultures. The project will include technological innovations and collaborations with research institutions and hospitals in France as well as abroad. The project consists in the original hypothesis that in the epileptic brain the bioavailabilty of anti-epileptic drugs is affected by P450 enzymes. The team and the new team leader are well prepared to address such challenging hypothesis. The laboratory researchers have sufficient expertise and creativity to face the competition with other groups working on the same line.

The project presents several original aspects of the research at the cellular and molecular levels using animal but also human samples. Three main aims are proposed:

- to determine whether seizure activities favor the expression of P450;

- to investigate whether the expression of brainP450 is under the control of specific ligand-activated transcription factors;

- to demonstrate that brain P450 enzymes metabolize anti-epileptic drugs.

If performed, this project should help to understand the why and how of some drug resistant epilepsies, and in a more general context its completion, should provide the way to exploit brain metabolic enzymes to bio-transform drugs into more efficacious compounds.

These objectives are both qualitatively and quantitatively ambitious but stay realistic although funding for some research lines are not secured yet, several applications to competitive national (ANR) grants are under evaluation.

Conclusion

The team is undergoing a transition and builds upon the expertise of both the former and proposed new team leader to address mechanisms dealing with the bioavailability of anti-epileptic drugs. The hypothesis is original and the panel advises the team to carry on all possible efforts to increase the visibility and demonstrate the relevance of this project.

- **Strengths and opportunities:**

During the past 5 years, the scientific output of the team at the IGF had been very good with a regular and a good level of publication.

The proposed new leader of the team has a solid scientific background and a very good experience of the interface between basic and clinical investigations.

Up-to-now the funding of the research has been provided by grants obtained from national institutions and a pharmacological company.

A significant number of students have been involved in the research performed by the team, including 4 PhD defenses.

- **Weaknesses and threats:**

There is no new funding listed for the 5-year coming period, this point should be addressed in the near future. In addition it appears that the team has attracted only one postdoctoral fellow during the evaluated period and there is no new postdoctoral fellow listed for the coming period. An effort to attract foreign candidates should be done.

- **Recommendations:**

During the past period, the team had a good background in publications, funding and formation. The integration of the new proposed team leader will be one of the keys for the future success of the team project. The future is rather uncertain as there is no funding announced for the coming 5-year period except the NIH funding of the proposed new team leader that is transferred to the IGF team. The project is ambitious and promising in the sense that it could provide original clues for the use of brain metabolic enzymes to transform pro-drugs into more efficient compounds. Finally, collaborations should be developed within the IGF with teams working on other brain pathologies for which a similar therapeutical strategy could be tested.

Team E03: Development of Cerebellar Gabaergic Circuit

Name of team leader: Mr Fabrice ANGO

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	1	1
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**3**	**2**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	2	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	1	1

• Detailed assessments

Assessment of scientific quality and outputs

The team was created in 2009 when the principal investigator (PI) received an ATIP/AVENIR grant. The team worked in the developmental neurobiology field on cerebellum as a model. Two projects were developed. One was aimed at understanding at the molecular level whether and how group-I metabotropic glutamate receptors (mGluRs) can modulate NMDA receptor activity since a physical link exists between these receptors through a Homer-Shank multi-protein scaffold. The team investigated the issue by using biochemical, electrophysiological and molecular biological approaches in cultured mouse cerebellar neurons. The team found that Homer1a or dominant negative Shank3 mutants that disrupt the physical link between the receptors allow inhibition of NMDA current by group-I mGluR agonist. Moreover, co-immunoprecipitation experiments showed interaction between G-protein βγ subunits and

NMDA receptor in the presence of Homer1a and group-I mGluR agonist. Altogether this constitutes a piece of data published in Plos One (2010), unraveling a new molecular mechanism by which group-I mGluRs could dynamically regulate NMDA receptor function.

The second project, in line with the PI postdoctoral work, was aimed at discovering molecular mechanisms underlying axon branching at specific and strategic locations during the formation of neuronal circuits. Their data tends to demonstrate that basket cells and stellate cells, that constitute distinct cell types of cerebellar GABAergic inter-neurons exhibiting differences in their subcellular target innervation, deploy different cellular and molecular mechanisms to achieve their distinct axon arborization and innervation patterns. In one study initiated during the PI post-doctoral stay (Plos Biology, 2008) (PI first author), evidence is shown that in the developing cerebellum, stellate axons are organized in characteristic trajectories and guided to Purkinje dendrites by the Bergman glia fibers; in addition, the PI showed that the IgCAM CHL1 contributes to the patterning and subcellular organization of stellate axons and innervation. The data are interesting because they also reveal that astroglial processes, by organizing the axon trajectory of GABAergic inter-neurons, contribute to the establishment of patterns of connectivity in complex circuits. This raises the question of whether this mechanism can be generalized. In another study (Current Biol. 2013), fully carried by the team, the role of Sema3A secreted by Purkinje cells in basket axon terminal branching in the Purkinje cell layer was examined. The team convincingly showed that inactivating Sema3A or the binding domain of Sema3A receptor induced a significant reduction of the stereotyped branching pattern of basket axons whereas a gradient of Sema3A induced local terminal branching of GABAergic axons that was dependent on the neuropilin 1 receptor. Importantly, the team showed that Sema3A triggered the activation of a novel Fyn signaling pathway that regulates the membrane localization of soluble guanylyl cyclase in the growth cone.

The scientific production of this small team that invested efforts in setting up appropriate models and tools is moderate but of high level and competitive in the field. The model is original and well chosen and the data answer some important mechanistic questions on axon guidance, branching and synaptogenesis while opening new avenues of research.

Assessment of the team's academic reputation and appeal

The PI was awarded several highly competitive grants at the national level. The team is still young but has acquired some visibility and appeal despite the fact that developmental neurobiology is not the hallmark of IGF; it recruited a post-doctoral fellow on a FP7 reintegration grant. The PI had been invited for presentations at one national meeting and several seminars in research institutes in France, Germany and USA. The PI is also a member of two evaluation committees (France and USA) and reviewer for Frontiers Synaptic Neuroscience, EMBO J, J. Neuroscience, PlosONe.

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

So far the team is fully committed to fundamental research.

Assessment of the team's involvement in training through research

During the past 5 years, the PI defended his HDR and 2 theses have been defended, two are in progress. The team also trained 7 master students.

Assessment of the strategy and the five-year plan

The scientific project is in direct line with ongoing and previous work of the team. A major challenge in the field is to elucidate how axons of specific neurons, in the complex *in vivo* environment of the cerebellum, can integrate multiple extracellular guidance cues and intracellular signaling pathways necessary for appropriate responses during wiring of circuits. The project aims at characterizing the early events of axonal development, branching and synaptogenesis of cerebellar GABAergic interneurons and at identifying the role of relevant CAMs in these processes. The project is based on a series of experimental approaches developed and mastered in the team. They consist in the use of transgenic mice with fluorescent neuronal subpopulations, the grafting of labeled neuronal progenitors in wild type or mutant mouse and performing high-resolution imaging approaches on slices.

The project has three objectives:

a) 3D reconstruction and morphological analysis of GABA interneurons;

b) Two-photon imaging of acute cerebellar slices and quantification of specific branch dynamics;

c) Electrophysiological properties of identified GABA interneurons during development.

The project is timely and competitive and the team has the competence to do it. Risk is well balanced as the preliminary data shown during the presentation support the feasibility of the two first objectives. One of the strengths is the dynamic imaging approach.

Conclusion

This is a very small team, very well-funded up to now, that targets an important research area in developmental neurobiology. The experts committee however felt concerned that the research theme is not fully integrated in the major research axes of the institute.

- **Strengths and opportunities:**

- so far well funded junior team mastering an original model well suited to answer the questions;

- mastering of the needed technical approaches including dynamic imaging of cerebellum slices;

- recruitement of a post-doctoral on a FP7 reintegration grant;

- access to IGF facilities and outstanding equipment.

- **Weaknesses and threats:**

The group is still small and visibility does not yet fully match the quality of the work. The recent publication should help the PI to get more invitations.

No grant secured for the future; funding should be actively searched.

- **Recommendations:**

The team needs to ensure that the profile of the research is promoted as aggressively as possible and make all efforts to increase international visibility. The team could perhaps benefit from taking advantage of the existing specific competences in the institute to develop collaborative projects as, for example, the one discussed during the interview on imaging the mobility in membranes of Semaphorin receptor components.

Team E04: Functional genomics of imprinted genes

Name of team leader: Mr Laurent JOURNOT

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	3	3
N3: Other permanent staff (without research duties)	3 (2)	3 (2)
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**6 (5)**	**6 (5)**

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

• Detailed assessments

Assessment of scientific quality and outputs

The team has performed excellent work regarding the transcriptional co-regulation of imprinted genes. They have shown that all imprinted genes, which are involved in very diverse functions, belong to a single gene network placed under the control of common regulators (Zac1) and specific genomic regions (Dlk1-Gtl2 locus). More recently, the team has shown that imprinted gene network (IGN) execution was instrumental in the process of corticogenesis (PNAS 2009, Nature 2008). Team members are managing the Montpellier genomics platform (MGX) and thereby play a key role in many research programs of the IGF and other groups of the Montpellier area. The efficiency of this platform attracts also collaborations from other parts of France and abroad.

Both quantitative and qualitative scientific production of the team is very good for a team of 2 full time scientists, 4 engineers/technicians and 3 post-docs/PhD students. During the past 5 years, there were 2 original publications with team members as first/last authors, 11 original publications from collaborative works and 2 reviews, in journals with very good to excellent impact. Two manuscripts reporting the recent team activities have been submitted recently. The energy spent by the team in the management of the MGX platform is clearly detrimental to the progress of its own programs, and collaborative publications are on average published in better journals than the original contributions of the team. Also, collaborative studies from the MGX platform published in journals such as Cell, Plant Cell, Nat Struct Mol Biol or PNAS were signed by platform members but not by team members and are therefore not considered here above.

Assessment of the team's academic reputation and appeal

The team has an excellent academic reputation and has published in the past in the best journals (Nature, Dev Cell…) highly cited publications (team leader h index: 27, > 4000 citations). The team leader is regularly invited to national and international meetings and seminars. He has also organized two international and one national meetings. Recently, the team leader has taken the task of scientific manager of BioCampus, which supervises 51 facilities in the Montpellier area, and as said, the team is operating the genomics platform MGX through which major grants were raised and new technologies (NGS, bioinformatics…) were developed. One scientist has been hired by INSERM in 2009. A group of biostatisticians will join the group in the next term and an Australian researcher with excellent reputation in the field will apply for a CNRS or INSERM position to work in the team.

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

The leader of the team shares the responsibility of coordinating local facilities (MGX) and is the local coordinator of several international programs. Two grants were obtained with private companies as partners. Members of the team are giving talks in public conferences during the “Brain awareness week”.

Assessment of the team's involvement in training through research

The team has trained 5 PhD students and 6 graduate students since 2009. The team is involved in lecturing in both cognitive and applied biology. Team members organize several yearly workshops and practical training courses on different aspects of genomics (Epigenomics, RNASeq, statistics…).

Assessment of the strategy and the five-year plan

The scientific project is a continuation on the ongoing project with 5 specific points:

1) mechanistic of the IGN (emphasis on the implication of the discrimination between quiescence and differentiation);

2) mechanistic of IGN co-regulation during re-entry into cell cycle of quiescent cells or exit from it for proliferating cells;

3) role of IGN in differentiation/ quiescence during adipogenesis and neurogenesis;

4) evolutionary view of the IGN;

5) statistics for genomic data, the latter project being linked to the implication of the team in MGX (Montpellier GenomiX facility).

The project is well written and original with an overall consistency even with point 5. Its feasibility in the next 5 years is obvious.

Conclusion

- **Strengths and opportunities:**

The team has an excellent background and a strong and original scientific project. This project is based on previous data obtained recently by the group and has high potential cognitive impacts. The team has privileged access to facilities and outstanding technologies and equipment, which is highly valuable to the project.

The arrival of new people with complementary skills will certainly be a major asset for the team.

- **Weaknesses and threats:**

The project is ambitious, especially as the team leader is deeply involved in the management of facilities (BioCampus) and several team members are in charge of the MGX facility. The output in terms of original publications from the team program itself is lower than previously and outnumbered by the result of excellent collaborative works.

- **Recommendations:**

The team has developped an original research and in the past years acquired the technology to continue this work efficiently. The team leader has done an excellent job in managing the Montpellier BioCampus and the MGX platform. This is however detrimental to the team programs, and the situation should remain transient. Therefore, the team leader should be helped in his platform management activities. A deputy director should be nominated to assist him in the immediate future, and take over the direction of BioCampus later on.

The team should pay attention to its project leadership and balance better its own projects with its work as a technological platform support.

Team E05: Functional neuroproteomics of neurological and psychiatric disorders

Name of team leader: Mr Philippe MARIN

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	4 (1,75)	3 (1,25)
N2: Permanent EPST or EPIC researchers and similar positions	4	4
N3: Other permanent staff (without research duties)	4 (3)	4 (3)
N4: Other professors (PREM, ECC, etc.)		1 (0,50)
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**15 (11,75)**	**12 (8,75)**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	4	
Theses defended	7	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	4	4

• Detailed assessments

Assessment of scientific quality and outputs

During the last 5 years, the major contributions of the team consisted in:

- I) the description of new mechanisms controlling G protein-independent receptor-operated signaling and underlying receptor-mediated activation of the non-amyloidogenic pathway;

- II) the identification of signaling pathways (mTOR and Cdk5) involved in the control of cognition and neuronal differentiation by 5-HT6 receptors;

- III) the demonstration of a role of 5-HT2A-receptor-associated PDZ proteins in diabetic neuropathic pain;

- IV) the characterization of extracellular biomarkers of neuronal apoptosis.

The team members are authors or co-authors of 47 articles in peer-reviewed journals: team members are the first or last authors on 15 among 34 original articles. Several manuscripts were published in journals with impact factors > 5: EMBO Mol Med, J Neurosci, J Biol Chem, Mol Ther and EMBO J. Two researchers of the team also participated in a collaborative Nat Neurosci publication (Bertaso et al., 2008) with the E02 team. One European patent was filed. Clearly, the scientific quality and output of this team are excellent.

Assessment of the team's academic reputation and appeal

The team has an excellent academic reputation and appeal. It is also internationally well recognized for its expertise in the serotonin system using proteomic approaches. Over the elapsed 5 year period, team members received 37 invitations including lectures at the Gordon Conference. The group has also organized the International Serotonin club meeting (2012) and co-organized the SMAP 2011 and SFEAP 2012 meetings. The team leader is the scientific manager of the Functional Proteomics Platform and director of the Proteome Pole. Other achievements of a senior member were the Chairing of the ANR Neuroscience Committee and Pôle Biologie-Santé François Rabelais and the participation to the National Expert Committee 24 of CNRS. A team member was awarded "Chercheur d'avenir" in 2011 and received the Junior Faculty Award at the International Alzheimer and Parkinson Diseases conference in 2013. The team which belongs to the Labex EpiGenMed was also recognized as a Fondation pour la Recherche Médicale (FRM) Team in 2005 and 2009. An additional proof supporting the strong international appeal of the group is the attractiveness of young foreign fellows and researchers.

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

Interactions of the group with the social, economic and cultural environment are excellent. In particular, there is a long-term collaboration with a pharmaceutical company. Also, a team member is the coordinator of the FUI contract DiaTral (Diagnostic and Treatment of Alzheimer's Disease) involving 2 pharmaceutical companies and Montpellier Hospital. The sub-project dedicated to biomarker discovery is coordinated by the team leader. Relevant is also the strong collaboration with a biotechnology company. This group also organizes social events during the brain awareness week.

Assessment of the team's organization and life

The team leader is the scientific manager of the Functional Proteomics Platform and director of the Proteome Pole.

Assessment of the team's involvement in training through research

The involvement of this team in training through research is outstanding. Several team members have heavy teaching duties while performing excellent research. More than 400h teaching per year are provided by the team members who also successfully trained 10 master and 8 PhD students over the elapsed 5 year period. It appears that the team leader and staff coordinate very well the group activities in order to create an excellent synergy and balance between full-time researchers and faculty members having teaching duties. Also, this group co-organized a proteomics school dedicated to interactomics with partners in Toulouse, Grenoble and Marseille.

Assessment of the strategy and the five-year plan

For the 5-year plan, the team intends to continue two major lines of research. The first one consists in the characterization of signaling pathways engaged by 5-HT2A, 5-HT4 and 5-HT6 receptors. The main objectives are:

1) the identification of molecular substrates of the psychoactive effects of hallucinogens and of their control by mGlu2 receptors;

2) the characterization of the molecular mechanisms underlying activation of the non-amyloidogenic pathway by 5-HT4 receptors;

3) the elucidation of signaling mechanisms involved in the control of cognition and of neuro-developmental processes by 5-HT6 receptors.

The second is fully exploiting the expertise in proteomics, and consists in the identification of novel candidate biomarkers of Alzheimer disease and multiple sclerosis (MS). The work will be carried out by 1) validating already identified candidate biomarkers and 2) the identification of biomarkers of MS conversion. To reach these goals, the project is organized into the 4 subprojects with a well-defined strategy and specific personnel dedicated to each subproject.

Conclusion

This is an excellent team highly recognized for its expertise in the serotonin system and led by a very dynamic and organized group leader. The team also plays a strategical role within the IGF through its expertise in proteomics, a kind of activity of central importance for the objectives of the institute.

- **Strengths and opportunities:**

- excellent environment of the IGF, state-of-the-art proteomic platform;

- excellent coordination of expertise and human resources to create an efficient synergy and balance between full-time researchers and faculty members;

- clinical collaborators.

- **Weaknesses and threats:**

Broad portfolio of projects which at some point will need to be carefully evaluated and prioritized.

- **Recommendations:**

The proposed developments are timely and promising. In a very competitive environment, this group should focus on its strengths. The experts committee trusts the team for quickly identifying the relevant points on which their project needs to be focused depending on the data obtained. Considering the work load resting on him the team leader might choose to seek some help/delegate tasks dealing with the management of the proteomic platform.

Team E06: Limits of neuroplasticity: anorexia and addiction

Name of team leader: Ms Valérie COMPAN

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1 (0,50)	1 (0,50)
N2: Permanent EPST or EPIC researchers and similar positions		
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1 (0,50)	
N6: Other contractual staff (without research duties)	1	
TOTAL N1 to N6	**3 (2)**	**1 (0,5)**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	3	
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	1	1

• Detailed assessments

Assessment of scientific quality and outputs

The main aim has been "to demonstrate that" 5HTR4 receptors belong to a decision network whether to eat after stress. For this, the team has developed a "translational neuroscience" approach. One last-author publication shows that loss of 5HTR4 aggravates long-term memory impairments caused by the muscarinic antagonist scopolamine (Segu et al, 2010). Another last-author publication uses localized nucleic acid delivery to show a role of 5HTR4 in the *Nucleus accumbens* in decreasing feeding, increasing motor activity, and in mediating reward responses of MDMA. The work provides some promising leads for human therapies, although a little caution is required in extrapolating from mouse behavior alone to the complexities of human eating disorders.

Altogether, there are five original research papers from the team in 5 years, including 2 as first/last author. The quality of the publications appears good, although citations are low so far for the first/last author papers, but the work appears to have been well received, e.g. judged by conference talks. However, the number of first/last author papers is low, given that the team leader has been in post throughout the review period.

Assessment of the team's academic reputation and appeal

Team members have made several oral presentations at international meetings, including the US Society for Neurosciences and have given several invited talks. The team has had an ANR grant and a number of smaller ones. An applicant to the team was awarded a Marie-Curie fellowship (although has not taken it up). The team has attracted other international visitors, including visiting academics and students in a joint scheme with Morocco. The team currently has a very good reputation and profile, although this will decline if they do not publish more.

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

The team leader has developed good links with industrial and non-academic partners, including 2 grants from a biotechnology company and generating two new patent applications. Being a scientific advisor for the biotechnology company she has communicated the work of the team to a public audience, using the suitability of the topic for raising public awareness of basic neuroscience.

Assessment of the team's involvement in training through research

The team has trained 3 PhD students to completion, two of them with a joint-first author publication in Translational Psychiatry. However, one PhD student recently changed to a different team and research project, by responsibility of the unit direction and there are presently no more PhD students in this team. The team leader has had good input into local Neuroscience training at Université de Nimes.

Assessment of the strategy and the five-year plan

Future strategy is focused strongly on NAc 5HTR4 “psychiatric” and neuronal phenotypes in mouse models, to test the role of abnormal neural connectivity between brain structures of the reward and stress pathways in eating disorders in animal models. The first aim is to test whether locally enhancing constitutive activity of 5HTR4 provokes sustained anorexia, the second is to examine morpho-functional changes due to 5HTR4 activity in neurons that express the receptor, e.g. using 5HTR4-GFP promoter fusion mice, the third is to assay whether such changes are also accompanied by increased communication between *Nucleus Accumbens* and ventral medial prefrontal cortex (mPFC).

In the short/medium term, the focus on 5HTR4 is justified because it builds on the team’s existing expertise, although the rationale and importance of some later aims needed better explanation. In the medium/longer term, a focus on a single receptor will limit the team’s scientific innovation. Although some transcriptomics work is proposed to go beyond this and the team also proposes translational clinical and industrial approaches, and there is clear potential for these, they were explained only briefly. It will be challenging to make progress in all the proposed work with a small team and it was not clear how different aspects of the work would be prioritized.

Conclusion

Very small group strongly engaged with industrial partners. Although the team is working on an important area for clinical translations very few significant scientific accomplishments were made.

- **Strengths and opportunities:**

- an important area for clinical applications and quality of life as well as scientifically;

- good experience in a relevant model system, backed up by some respected publications; a well-regarded reputation and profile;

- engagement with industrial partners.

- **Weaknesses and threats:**

There are not yet enough first/last-author papers to create a sustainable research program for the team.

In the short-term the focus on a single protein is understandable but in the longer term this will be limiting. Also there is not a strong sense of how different parts of the proposal would be prioritized for further development, and relate to each other.

- **Recommendations:**

Numbers of first- and last-author/corresponding author publications must increase. The team leader also needs a clearer vision of her basic mechanistic goals, including a better vision of how different parts of the proposal contribute to her long-term goals, and better prioritization of individual goals, mindful of the size of the group.

Team E07: Normal and pathological neurobiology of Drosophila

Name of team leader: Ms Marie-Laure PARMENTIER

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	5	5
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**8**	**6**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	3	
Theses defended	4	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	3	3

• Detailed assessments

Assessment of scientific quality and outputs

The team's publications cover a number of areas in *Drosophila* neurobiology and neuropathology, principally: GPCRs and chemosensation; the developmental role of Engrailed protein; and the normal functions, pathomechanisms, or protection against pathology, of disease genes including dystroglycan, huntingtin/polyglutamine, and tau. These results are published in very good journals, including an outstanding pioneering one in PLoS Biology on the first insect GPCR identified to have a role in taste. Among their other work the 2011 HMG tau publication has interesting implications for therapies based on inhibition of tau phosphorylation; the team has also identified proteins and peptides that can protect against the toxic effects of mutant huntingtin.

From 2008-2013, the team published 15 original research papers, 9 of them as first or last authors. The major publications are being well cited, especially the PLoS Biology one and their 2008 PLoS ONE publication on the synaptic role of dystroglycan.

The team has seen some changes in structure and emphasis. One researcher and her group joined the team from IGH in 2011, but recently left for an academic position elsewhere. The current team leader took over in 2011 and is overseeing a stronger focus on the role of the cytoskeleton in synaptic function.

Assessment of the team's academic reputation and appeal

The group has a strong reputation in *Drosophila* Neuroscience. The chemosensory GPCR publication was recognized by F1000 and the team leader is on the editorial/reviewing boards of PLoS ONE and European Journal of Neuroscience. Their track record and expertise has put them in demand as collaborators, both from France and abroad including Hong Kong, China and Germany. It is hosting a sabbatical visitor from Brown University, USA. The team leader was selected as Chercheur d'avenir (2011), another team member held an ANR grant for €250k, and the team attracted an overseas graduate student (China) and a postdoc (Russia)

The excellent primary research productivity is reflected by 24 seminar invitations or presentations at French meetings for team members and an international meeting organised by the team leader, although only by two talks at international meetings. Their primary productivity is also not reflected by any high-profile international review articles or chapters.

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

The team has a very good track record of interactions with industrial companies. They were awarded a significant €310k from FUI Program DiaTral with a pharmaceutical company for tauopathy work. Their GPCR taste receptor shows some promise for development of novel insect repellents and initial patent protection was granted for this, although surprisingly it was not possible to obtain further funding to exploit it. A further patent application for Huntington's disease therapy has been filed. The team also makes annual presentations to schools and the general public.

Assessment of the team's involvement in training through research

The team had 4 PhD theses successfully completed in 2008-2013 and 3 in progress; completed PhD students whose papers appeared in the current period all obtained first-authorships and usually additional co-authorships. The team leader obtained her Habilitation in 2010. Team members contributed around 130h teaching at Master level.

Assessment of the strategy and the five-year plan

Under its new (since 2011) team leader, the team is now choosing to focus on their interests in the roles of cytoskeletal proteins in synaptic function and degeneration. The team proposes a number of closely related projects:

- one is to understand the roles of microtubules and their binding proteins in presynaptic function (manuscript under revision);

- the second is to use their system to study the *in vivo* role of polyglutamylation and its collaboration with an IGH group is a good use of local complementary expertise;

- the third is to develop the adult Neuromuscular junction (NMJ) as a system to study neuronal ageing, which is not possible in the widely used larval system, and where the 60-day ageing fly has some advantages for tau studies over more slowly ageing mice; in addition they are using genetic screening to identify new determinants of human tau toxicity in flies.

This level of focus is about right, it uses materials and methods that the team have demonstrable expertise in, builds on their existing published work, and shows awareness of the implications for human pathology and therapies.

Although the team is the only Drosophila group in IGF, their interests are appropriate for IGF and they interact closely with other local fly groups and share some facilities with IGH.

While the group has made the right decision on its proposed focus, an unfortunate consequence is that it has not been possible to continue their pioneering chemosensory work, in spite of considerable attempts to fund it.

Conclusion

Very good team with a strong reputation in Drosophila Neuroscience, now changing in structure and emphasis.

- **Strengths and opportunities:**

An excellent publication track record; very original work both published and in progress; a clear focus for the coming period; potential for novel mechanistic insights into tauopathies; a strong local fly community.

- **Weaknesses and threats:**

International visibility should be higher and is easily achievable given the track record. Limited external funding, and smaller team size since departure of a senior researcher, could ultimately limit the ability to build on the successes and develop new areas. The team could develop more interactions with mammalian or human groups.

- **Recommendations:**

- continue the current primary focus on tau and cytoskeleton;

- increase international visibility through international conference talks and high-profile reviews;

- obtain additional external funding;

- attracting a nearby team with potential for collaboration might be considered, if both teams would benefit from proximity;

- explore more interactions with mammalian or human groups with similar or complementary interests.

Team E08: Physiopathology of pancreatic ß-cells

Name of team leader: Mr Stéphane DALLE & Magalie RAVIER

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1 (0,25)	1 (0,25)
N2: Permanent EPST or EPIC researchers and similar positions	3	3
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**7 (6.25)**	**4 (3.25)**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	2	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	2	2

• Detailed assessments

Assessment of scientific quality and outputs

This team has studied during the past 5 years intracellular pathways regulating pancreatic beta cell survival and apoptosis. They demonstrated the role of arrestin-1 downstream of the pro-survival PACAP and GLP-1 receptors and the contribution of CREB transcription factor degradation in in glucotoxic conditions, and identified a kinase controlling the inflammatory action of cytokines on beta-cells. The scientific production by the team is excellent with 5 original publications as first/last author (Diabetes 2x, PNAS, JBC 2x), 7 original publications as coauthors and 3 reviews. The publications by one of the team leaders are the products of her post-doctoral period abroad, but there are also two very good publications from the local team over the last 5-year period. Current work focuses on metabolic stresses (gluco- and lipo-toxicity) in β-cell models (cell line) as well as in human islets.

Assessment of the team's academic reputation and appeal

The team has a strong reputation in the field. Team members are regularly invited to meetings and for seminars, although mostly in France. Team co-leader organized an international meeting with a pharmaceutical company and team members are experts in diverse French and foreign funding agencies. Team leaders were coordinators of 2 SFD grants and an INSERM-Avenir grant, and partners of 3 ANR and an FP7 grants. They both received a scientific prize during the past 5-year period.

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

The team has interactions with several pharmaceutical companies and obtained 3 grants involving private companies. One of the team leaders filed a patent in 2012 and is presently launching a start-up company based on this patent and the use of human islets, with the help of SATT. Because of confidentiality issues related to the molecular targets, it was not possible to evaluate this part of the project. Team members created a facility for human pancreatic islet isolation in 2009.

Assessment of the team's involvement in training through research

Two PhD theses and one HDR were defended during the past 5 years, which is fine for the size of the group. The team members teach in Master programs in Montpellier and Lyon.

Assessment of the strategy and the five-year plan

Taking into account the expertise and projects of the present leader plus the excellent training of the recently recruited co-leader, this team has an excellent and promising plan for the coming years. The projects constitute the follow-up of previous studies, and incorporate an innovative and potentially highly valuable aspect on GLP-1 resistance. The team will pursue its studies regarding the signaling pathways activated by GPCRs (i.e. GLP-1 receptor), tyrosine kinase receptors (insulin receptor) and glucose, and their interactions, particularly in prediabetic and diabetic conditions, focusing onto the role of β-arrestin isoforms on the control of insulin secretion and β cell mass. Human β cells as well as mouse models with β cell-specific inactivation of β-arrestin genes will be used, and the dynamics of receptor trafficking and protein interactions will be studied. Changes in GLP-1 signaling will be investigated in conditions known to modify the expression of β-arrestins (free fatty acids and corticosteroids). The effect of chronic glucagon receptor stimulation onto β cell responsiveness to insulin and GLP-1 will also be investigated. These latter aspects seem the most promising.

Each of the co-leaders will direct complementary parts of this interesting program. The project is highly dependent on the regular access to human β cells originating from the facility that will also provide β cells to the start-up company resulting from the previous activities of the team.

Conclusion

- **Strengths and opportunities:**

The team has solid expertise and reputation, and the projects are excellent. There is an appropriate balance of senior versus junior members in the team. The combination of basic and one applied research is interesting if the two aspects develop well in harmony.

- **Weaknesses and threats:**

Potential issues related to the two-head format of the team may arise. One of the co-leaders is expected to concentrate on basic research in the IGF team, while the other should run more applied research in close collaboration with the spin-off company. If the creation of the company is not successful, there might be competition for the leadership of the basic research program.

Both the company and the research team will need access to the limited resource of human pancreatic islets. This may lead to conflicts of interests, particularly if the company is very successful and can afford unlimited funding of this resource.

- **Recommendations:**

It would be useful to delineate better the respective projects and responsibilities of each co-leader, in particular in the event the start-up would face problems.

Team E09: Neuroreceptors, Dynamics and Function

Name of team leader: Mr Jean-Philippe PIN and Mr Laurent PREZEAU

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	5	5
N3: Other permanent staff (without research duties)	4 (2,50)	4 (2,50)
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	12	4
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**21 (19.5)**	**13 (11.5)**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	3	
Theses defended	12	
Postdoctoral students having spent at least 12 months in the unit	5	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	4	4

- Detailed assessments

Assessment of scientific quality and outputs

This is a well-established team that has worldwide reputation for his landmark and pioneering findings on the mechanisms and pharmacology of class C GPCRs, a key family of intercellular signaling receptors. The team provided original and important concepts regarding the molecular operation of these receptors, their architecture and oligomerization, their dynamics, their pharmacological regulation by orthosteric and allosteric ligands and their therapeutic potential in CNS diseases. The team has also a long and successful history of research and development by developing innovative technologies (including time-resolved FRET sensors) to study membrane receptors structure, stoichiometry and dynamics, and for drug screening applications. The scientific production is excellent both in quantity and quality with 6 patents and 18 publications from the team, 26 in collaboration). Publications are in high

impact journals (PNAS, EMBO J, Nat Chem Biol, Nat Methods, FASEB J…). The team leader has an impressive citation index (h=62; total citations > 16000). The team co-leader has a strong track record (h=32; total citations > 4000). The team has established excellent local, national and international collaborations both with academic and industrial partners. Overall the scientific output and productivity is outstanding reaching the highest international standards.

Assessment of the team's academic reputation and appeal

The team has high reputation and very strong worldwide visibility. The team leader, who is also head of the Institute, has very strong national and international visibility being regularly invited to speak at the most prestigious international conferences (Gordon, Keystone), as well as top universities and research centers. The team leader has been and is a member of several scientific committees (Commission Neuroscience INSERM) and journal editorial boards (JBC, EJN, Molecular Pharmacology, EJP) and has organized several international meetings including one Keystone meeting and one Gordon Research Conference. He has also recently obtained several prestigious prizes including the silver medal from CNRS and the Grand Prix Leon Velluz from the French Academy of Sciences. All the senior scientists of the team have also a strong reputation in their field. The team is highly attractive and new PhD students and postdocs are recruited on a regular basis.

The fund raising activity is also excellent (Equipe FRM 2013, several ANR grants, several industrial contracts) as well as the participation to important national (founding member of the Labex EpiGenMed) and international (2 Eranet Neuron grants) programs.

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

The team developed strong and fruitful links with industry, and has been instrumental in the creation in 2009 (still ongoing) of a CNRS-industry collaborative laboratory between IGF and a biotechnology company. Funding from industrial partners has been regularly obtained. The team leader is a consultant for another biotechnology company. The team validated mGluR4 as a novel target for the treatment of Parkinson disease and chronic pain, a discovery that has important implications for future therapeutic developments. The team co-leader is head of the ARPEGE Pharmacology platform facility devoting a significant fraction of his time to run and manage the facility. The platform, which is open to external partners including private companies, proposes state-of-the-art technologies for ligand binding, drug screening and cellular signaling assays. It has obtained the national IBISA label in 2008, and since 2012 is part of the CNRS UMS 'Biocampus'. Overall, these activities are excellent and have a very positive impact on the Institute attractiveness and reputation.

Assessment of the team's involvement in training through research

The team is highly dynamic with several PhD students and postdoctoral fellows, several from abroad. Since 2008, eight graduate students defended their PhD and three started their PhD program. During this period, the team also recruited two permanent researchers, two researchers were promoted as Directeur de Recherche (DR) and two obtained their Habilitation à Diriger des Recherches (HDR). Both team co-leaders participate to teaching activities at various universities. As a whole, the research training and teaching activities are excellent.

Assessment of the strategy and the five-year plan

The projects are in line with the current strategy of research and aims at:

I) elucidating the molecular and structural bases of ligand action at class C GPCRs;

II) probing their conformational changes and structural dynamics;

III) deciphering the importance of oligomerization in the signaling properties with a special focus on determining the functional roles of oligomerization *in vivo*;

IV) developing innovative tools and assays to examine class C GPCR functions;

V) identify and develop novel ligands for mGluRs and evaluate their therapeutic potential.

Towards these aims, the team proposes to combine multiples approaches including receptor engineering and purification, design of novel pharmacological ligands, development of original bio-sensors, single-molecule analysis, nanobodies, opto-reactive ligands, implementation of innovative microscopies etc. The objectives are well thought-out and the various approaches/tasks well defined, each supervised by a senior researcher of the team. No major issue regarding feasibility is expected given the strong expertise of the team, the synergy between the various axes and the very good level of funding. The project will also benefit from several established national and national collaborations with scientists both from academia and industry. Overall, this is an excellent project, highly relevant and with important objectives which are likely to maintain the leading international position of the team.

Conclusion

Excellent team among the leading international research groups in the field of molecular pharmacology and molecular and cellular neuroscience, with cutting edge projects.

- **Strengths and opportunities:**

As a whole, the team is of outstanding quality. It is one of the leading international research groups in the field of molecular pharmacology and molecular and cellular neuroscience. It has provided key contributions in the field, implemented a impressive set of techniques and contacts with industrial partners, and proposes strong and ambitious projects. This team has consistently demonstrated its ability to carry out research at the highest international standards.

- **Weaknesses and threats:**

There are no obvious weaknesses.

- **Recommendations:**

Maintain the level of excellence.

Team E10: New Ion channel families

Name of team leader: Mr François RASSENDREN

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1 (0,50)	1 (0,50)
N2: Permanent EPST or EPIC researchers and similar positions	2	3
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**5 (4.5)**	**5 (4.5)**

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

• Detailed assessments

Assessment of scientific quality and outputs

The team research focused on two axes: 1-characterization of molecular determinants of P2X receptor (P2X-R) complexes and 2-Understanding of physiological functions of P2X-R. Although the critical mass of this team was very small during the elapsed 5 year period, the group published 10 articles in peer-reviewed journals with 5 year impact factors higher than 5. Team members are first or last authors on 5 original articles. This group demonstrated that P2X4 is expressed *de novo* in microglia in neuropathic pain model, where it contributes to BDNF release (J Neurosci 2008), whereas it contributes to PGE2 from tissue resident macrophages in inflammatory pain (Embo J. 2010). Also, the group showed that the induction of a *status epilepticus* induces a particular type of microglial activation characterized by an enhanced purinergic signalling (J Neurosci 2008). Data from the team also revealed that P2X4

regulate specific functions of activated microglia and contribute to CA1 hippocampal neuronal death (Glia 2013). Recently, the group demonstrated that P2X2 and P2X5 subunits form a new heteromeric receptor with 2 potential stoichiometries (J Neurosci. 2012). A collaborative work with Khakh BS (UCLA) showed P2X2-R regulation by VILIP1 (Sci Signal 2008). Clearly, the scientific quality and outputs of this team are excellent.

Assessment of the team's academic reputation and appeal

In spite of its small size, the team has an excellent academic reputation and appeal. Indeed, the group is partner in different national research program supported by ANR. Team members have also fruitful international collaborations with a laboratory at UCLA and several other groups working on purinergic signaling. Moreover, the team is part of the labex ICST (Ion Channel Science and Therapeutics). The team leader has organized two international symposia. He is frequently invited for international meetings on purine. Also, the team leader has been contacted as expert/reviewer by National and International Funding Agencies including ANR, Welcome Trust and BBSRC.

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

The team has no formal collaboration with the industry. However, it developed close link with a pharmaceutical company, particularly in the field of transcriptome analysis and of P2X4 receptors in pain processing. Also, the team provides counseling to a biotechnology company in the field of purinergic receptor and ligand-gated channels. These interactions seem interesting but the team seriously needs to improve its interactions with social, economic and cultural environment.

Assessment of the team's involvement in training through research

The team leader is involved in teaching for master students (Master Biomed P3.1, UE Methodology). He is the co-chair of M2 student Journal Club and the organizer of a training session for a pharmaceutical company. One graduate student defended his PhD thesis in the group and another one has just started. This point also needs to be improved in the next period by increasing the number of PhD students and the number of qualified supervisors having the HDR.

Assessment of the strategy and the five-year plan

A central hypothesis of the group is that in myeloid cells, both P2X4-R and P2X7-R belong to the same signaling platform and act synergistically to shape inflammatory responses. To check this idea, the team defines a strategy with two main research axes:

I) molecular characterization of interactions between P2X4 and P2X7 receptors;

II) determination of the role of P2X4 and P2X7 receptors in chronic disease such as pain or neurodegeneration.

All expertise and technological tools to reach their objectives are well identified (resolve fluorescence, FRAP or single molecule imaging, collaborative studies with different teams for DNA immunization to produce specific monoclonal antibodies or nanobodies, fluorescent-based screening assays, proteomic approach based on immunopurification of the complex in bone marrow-derived macrophages, mass spectrometry, flow cytometry, conditional P2X4 null mice, P2X7 deficient mice etc). The strategy and plan sound interesting and promising.

Conclusion

Excellent team well equipped conceptually and methodologically, developing an original well-structured project.

- **Strengths and opportunities:**

Excellent environment of IGF, recruitment of a new full-time researcher to increase the critical mass and strengthen the team expertise and work capacity, collaboration with other teams to support the project.

- **Weaknesses and threats:**

Limited number of experienced senior investigators to well coordinate different subprojects (only one HDR), very low number of PhD students (only one), lack of industrial contracts/interactions to support technological transfer and valorization of the data.

- **Recommendations:**

Team staff should rapidly increase the number of senior investigators holding an HDR in order to recruit PhD students. Also, team members must negotiate with industrial partners official contracts allowing financial support.

Team E11: Membrane receptors: structure, dynamics and pathologies

Name of team leader: Mr Bernard MOUILLAC

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1 (0,25)	1 (0,25)
N2: Permanent EPST or EPIC researchers and similar positions	4	4
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**8 (7.25)**	**6 (5.25)**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	1	
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	3	3

• Detailed assessments

Assessment of scientific quality and outputs

The team is mostly focused on the study of vasopressin and oxytocin receptors. The goals of the team involved the characterization of new ligands with potential therapeutic interest, the study of receptor interactions with partners and the determination of GPCR structures. These receptors are therefore used as models for studying general aspects of GPCRs, including biased signaling and functional consequences of oligomerization.

One of the breakthroughs during the last years is the identification of the first biased agonists acting as pharmacochaperones for misfolded mutant forms of the Antidiuretic hormone arginine vasopressin (AVP) receptor. These molecules activate the cAMP pathway but inhibit arrestin-dependent internalization, with a significant potential

as therapeutic agents in nephrogenic diabetes insipidus. The development of other V2 ligands has also led to the filing of patent applications. A second breakthrough was the use of time-resolved FRET (a technique developed together with team E09) to demonstrate the presence of GPCR dimers in native tissues. Finally, another major contribution to the field of GPCRs was made by the recently recruited and proposed co-leader of the team. While visiting fellow in a laboratory at Stanford University, he determined the crystal structure of two members of the opioid receptor family.

The scientific output of the team is 24 original publications in peer-reviewed journals since 2008, 12 originating from the IGF with members of the team as first and/or last authors, and two with the new team co-leader as first or last author but originating from Stanford U. Among these publications, excellent and top journals such as Nature (twice), Nat Chem Biol, Proc Natl Acad Sci USA (twice), J Biol Chem, Mol Pharmacol, J Am Soc Nephrol. 14 publications result from collaborative work with other teams of the IGF of other structures. In addition, 13 review articles and two book chapters were published by the team. The publications reporting the main achievements described above have gathered significant citations records, acknowledging their impact on the scientific literature and their field.

Assessment of the team's academic reputation and appeal

Members of the team were invited to 36 international meetings during the past 5 years, among which 21 were held abroad. This reflects the international recognition of this team and its impact on the GPCR scientific community. During the same period, the team attracted 3 foreign PhD students and 4 foreign post-doctoral fellows. The present team leader is chair of the IUPHAR committee for vasopressin/oxytocin receptors, establishing his international leadership for this class of GPCRs and team members are experts for a variety of French and foreign funding agencies. The team has also maintained a large number of excellent and productive collaborations with various groups in the IGF, Montpellier, France and abroad. The team obtained three grants from ANR and two industrial grants. Both proposed leaders received the prize for scientific excellence from INSERM in 2012.

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

New ligands of the V2 receptor and a V2 antagonist identified in snake venom were protected by three patent applications. Two industrial grants were obtained by members of the team (shared with another IGF team). A strong and long standing collaboration has been established with the company CisBio Bioassays, specialized in the design of assays for receptors and signaling cascades. This collaboration has resulted in the co-development of widely used bioassays (IP One, Tag Lite, cAMP dynamic kit) and the creation of a CNRS-industry common laboratory in 2009. A number of ligands discovered in the team have a potential as leads toward the development of therapeutic agents for human diseases. In addition, the established GPCR structures may help in the rational design of new molecules.

Assessment of the team's involvement in training through research

Four PhD theses were defended during the past 5 years. Two members of the team obtained their “habilitation”. A team member is teaching in different doctoral schools in Montpellier, Strasbourg and Lyon. Several members are also involved in the institute training program “IGF formation permanente”.

Assessment of the strategy and the five-year plan

The team intends to pursue its ongoing research programs with the aim of better understanding the molecular and structural bases of GPCR coupling to different G proteins, scaffolding proteins and downstream signaling cascades. Two main groups of receptors will be used as models, the vasopressin/oxytocin receptors for which the group has a long standing expertise and many tools available, and opiate receptors for which the expertise has been imported with the integration of a new Principal Investigator in the team. In addition to being valuable models, both classes of receptors have a medical interest as drug targets and/or as the cause of human genetic diseases. The program is articulated in two complementary parts. First, the group will investigate how biased ligands can result in the differential activation of signaling cascades by a variety of approaches (STD and NMR on purified receptors) and how oligomerization affects coupling and signaling. The V2 receptor will be their primary model in this work, considering the panel of ligands and tools available in the group. Second, they will investigate structure of V2 and opiate receptors in different states, namely inactive and active forms, as well as complexes with G proteins and arrestin, using fluorescence and NMR spectroscopy and X-ray crystallography.

The project is clearly described and timely. It approaches important questions in the GPCR field, and the group has the necessary expertise to contribute much to the progress in these areas. The second part of the program, involving structural determination of GPCR (complexes) is obviously risky. However, the group has a strong expertise in receptor expression and purification, and the recent recruitment brings to the team a rare expertise in GPCR crystallization. Moreover, the group has a number of collaborations with outstanding GPCR groups around the world, among which a group at Stanford University, one at Duke University and one in Montreal. Altogether, the project is therefore ambitious but realistic.

Conclusion

- **Strengths and opportunities:**

Excellent scientific background of the team with an established international leadership on the oxytocin/vasopressin family of GPCRs.

Excellent recent recruitment, bringing in the group the necessary expertise in GPCR X-ray crystallography.

Significant opportunity to contribute to the very competitive field of GPCR structural determination, as a result of the combined past expertise of the group and the new expertise brought in by the recently recruited co-leader.

Strong and well-established collaborations worldwide.

- **Weaknesses and threats:**

X-ray cristallography of GPCR is (not yet) routine activity. There is therefore a risk for a medium sized group in investing much energy and time in such program.

Team E12: Cardioprotection : physiological and genetic aspects

Name of team leader: Ms Stéphanie BARRERE-LEMAIRE & Mr Matteo MANGONI

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	3 (1)	3 (1)
N2: Permanent EPST or EPIC researchers and similar positions	2	2
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	1
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**9 (7)**	**7 (5)**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	1	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	5	5

• Detailed assessments

Assessment of scientific quality and outputs

The research team is co-led by two team leaders since 2005. The research program covers two major fields of cardiac pathophysiology, each led by one of the PIs.

I) Mechanistic bases of cardiac rhythmicity and its alterations.

In the period 2008-2013, this activity produced several excellent to outstanding papers, partly in collaboration with renowned international groups. A major topic is pacemaking and its molecular basis, which is a remarkable topic of investigation. To this field, the group contributed with several new findings, highlighting the interplay of HCN channels with calcium channels (Cav1.3) thanks to a transgenic model (PNAS, 2009) and more recently, uncovering the

interplay with novel regulators of pacemaking, connexin30 (CVR, 2010) and TRP channels, with two articles published in PNAS and Circulation in 2013 in collaboration. Another relevant aspect concerns G protein activated K-channels as players in sinoatrial node (SAN) automaticity, which is the specific research focus in a recent publication (JGP 2013), and uncovers a physiological role for IKAch which has been neglected in the literature. The team also contributed several excellent to outstanding papers concerning the consequences of channelopathies involving calcium channels (Cav1.3) in the dysfunction of atrioventricular conduction or ryanodine receptor mutations (CPVT) in SAN dysfunction and bradycardia, with several papers including Nature Neuroscience (2011) and Circulation (2012).

II) Molecular and cellular basis of hypoxia/ischemia damage and cardiomyocyte survival.

The team investigates new targets for reducing or preventing cardiac damage occuring after an ischemic event. Studies on postconditioning unveiled the role of pro-apoptotic genes such as Zac1 and Daxx (CVR, 2012), by using a genomic approach. Functional studies have confirmed the hypothesis and led to a novel interpretation and estimation of the "window" allowing for longer cardioprotection which may have relevant consequences in the clinic (TCM, 2012). This led to a patent deposit with a World coverage extension thanks to an industrial partnership. The proof-of-concept underpinning this patent is interesting, since a single bolus of a specific inhibitor peptide targeting FAS-DAXX and FAS-FADD led to cardioprotection in a mouse model of acute infarction. A further interesting approach comes from the study of glutamate signaling as a protective mediator in postconditioning.

Overall, during the past 5 years, the team has implemented state-of-the-art techniques and produced 38 original papers (10 with team members as first/last author and 16 from collaborations), 17 review articles. The investigators demonstrated leader skills, ability to undertake new, original paths and hypothesis and to expand IGF's network by collaborations with prominent international teams. Of particular interest, together with the implementation of new techniques, is the capacity to apply their discoveries to different fields, as demonstrated by papers in neuroscience journals on Cav1.3 defects and deafness (2011), and more recently (in collaboration with E23), on mechanosensitive proteins in zebrafish, and by evidence of the involvement of glutamate signaling in cardioprotection.

Assessment of the team's academic reputation and appeal

- **Capability to attract resources**

One team leader participated to the Marie Curie ITN "CavNet", a highly competitive collaborative program within FP7. The other Principal Investigator was team leader in the national RIRE network on myocardial infarction. Also, the team obtained 7 academic grants and 2 industrial grants.

- **Reputation**

Both team leaders have excellent bibliometric indices in their field and a respected reputation, as demonstrated by invitations for lectures in international meetings (14) and seminars (12), and activity as grant and journal reviewers. Both principal investigators are members of the LabEx ICST (Laboratoire d'Excellence Canaux Ioniques d'Intérêt Thérapeutique), one is heading of the Physiology Department and is in the editorial board of JMCC since 2008. The other was awarded by the Fondation pour la Recherche Médicale in 2011.

- **Attractiveness**

The team trained 2 foreign post-docs and hosted 4 visiting scientists (2 senior, 2 post-docs). It has collaborative research within IGF and with national/international teams.

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

The team has significant clinical interactions, also thanks to the presence of clinicians in the team. Its research extends from basic to translational, and is driven by relevant clinical questions and often emerging from unmet clinical problems (eg, congenital arrhythmogenic diseases in humans, functional role of human mutations, new diagnostic traits for congenital diseases, proof-of-concepts and patent for new treatments in acute myocardial infarction).

One of the team leaders has a new innovation project with several companies, starting July 2013 on the cardioprotective peptides. A patent application with a World coverage extension thanks to an industrial partnership covers the use of these peptides. The team has two industrial grants with IRIS (Servier).

Assessment of the team's organization and life

The team staff is solid, consisting of the two team leaders, one staff scientist and two teachers from Université Montpellier. The team also includes presently two post-doctoral fellows and one PhD student. The team members demonstrated the capability to exploit the available resources in terms of research infrastructures for animal facilities and transgenic models, genomics, imaging, biotechnology and molecular biology in general. The team demonstrated to be open to new ideas and strategies, eg, in collaboration with other IGF groups (E23). During discussion, both team leaders reported to be fully satisfied by the present situation and willing to continue and reinforce co-responsibility of the team, also implementing new common projects.

Assessment of the team's involvement in training through research

During the last 5 years, the team carried out an intense activity of training through research as demonstrated by 6 PhD theses and 3 HDR defended. 7 post-doctoral fellows were trained in the team as well as 16 Master students. The effectiveness of supervision is demonstrated by joint publications (or manuscript in preparation) for all post-doctoral fellows recruited so far. Overall, the general impression is that this team is capable of involving students and fellows in interesting projects, also based on multidisciplinary approaches and international collaborations, promoting their progress toward independence and internationalization. Of particular mention is the very competitive ITN program carried out by one of the team leaders. The team has also several training and teaching activities in master courses, surgery training for animal experimentation, besides formal teaching in the school of medicine.

Assessment of the strategy and the five-year plan

The two team leaders propose three major fields of investigation for the next five years, on the basis of their expertise and pre-existing results:

1) identification of the functional role of ion channels in the generation of cardiac pacemaker activity and its regulation by the autonomic nervous system. This study emerges from the conclusions reached by the previous studies on the interplay among calcium channels (Cav3.1 and especially Cav1.3) and HCN in cardiac automaticity and particularly their dysfunction; it takes advantage of the availability of existing transgenic models or their expertise to set-up new ones. The original hypothesis is to overcome loss-of-function in “depolarising” currents by antagonizing GIRK4 activity with novel candidate drugs. The idea is based also on original findings, not yet published, that GIRK4 inhibition or silencing might be able to rescue Cav1.3 loss-of-function without gross alteration. In the same line, the team will attempt rescuing pacemaker activity by means of a biological pacemaker. This idea is not new *per se*, since such an approach has been pursued by several teams. However, the cell line used for this study is novel, consisting of pacemaker cells derived from a subpopulation isolated from skeletal muscle. A thorough characterization of these cells has been carried out in the team throughout a 3-year work, and a publication is under submission. It is an interesting approach due to the possibility of “homologous” cells from muscle biopsies, not undergoing intense manipulation as for iPS, and therefore prospectively of translational interest. The model used for this study will take advantage of the well-investigated transgenic models with impaired HCN4 or Cav1.3 -dependent regulation of pacemaking;

2) study of IR-induced cell death pathways and endogenous mechanisms of cardioprotection. This project also consists of two objectives. The first, is centered on the exploitation of the novel cardioprotective strategy consisting in peptide-mediated decoupling of the FAS-DAXX interaction and thus inhibition of the extrinsic apoptotic cascade leading to a 60 % decrease in infarct size. It is sound and reasonable, since the investigators – as mentioned - filed a patent on these peptides and thus it deserves an attempt to bridge the gap between clinical innovation with the generation of new, more specific (second-generation) peptides. To this purpose, both the involvement of a pharmaceutical company, allowing World coverage extension of the patent, and proof-of-concept in large mammals must be regarded with interest. The second objective relies on the recent demonstration of the involvement of glutamate signaling in cardioprotection emerging from transcriptomic approach. Of course, there are challenging parmacodynamics and pharmacokinetics aspects to be accounted for, due to the renown toxic effect of mGlu in CNS; from this point of view, the involvement of team E09 at IGF is relevant because of their experience on G protein-coupled receptors;

3) pharmacological and molecular regulation of heart rate and cardioprotection. This is a joint project led by the two team leaders, combining the pacemaking and cardioprotective field in a project aimed at investigating the

potential advantage of Cav1.3 blockade and therefore negative chronotropic effect on protection against ischemic disease. It stems from previous evidence that ivabradine – a bradycardic agent – exerts a global protective effect in ischemic cardiomyopathy and heart failure in animal models and in clinical trials. Novel candidate molecules are available as Cav1.3 blockers thanks to collaboration with a large pharmaceutical company. Overall this is an interesting project, which may lead to expected or unexpected results. This point has been further discussed and especially the expected advantages over the existing pharmacological therapies such as beta blockers and ivabradine. Besides testing in acute ischemia, it has been suggested to pursue also the investigation in chronic ischemia and remodeling.

Overall, the proposed research plan is based on sound preliminary results, availability of animal models and take advantage of facilities and collaborations within IGF, contribution by companies and offers prospectively some relevant impacts. The chance of getting novel interesting results is realistic and the specific outcome – to some extent – not completely predictable. This makes the program even more intriguing.

Conclusion

- **Strengths and opportunities:**

The team has a large experience, international reputation, a broad network, excellent to outstanding publications. It demonstrated its ability to implement novel models and experimental approaches using a broad spectrum of technologies. It has good clinical collaborations and joint programs with other IGF teams. Of note, their translational approach and the capability to interact with companies thus bridging the gap between basic research and clinic innovation in the field of cardioprotection.

- **Weaknesses and threats:**

Both team leaders are involved in fields characterized by intensive research during the last 3 decades and, sometimes, disappointing results when translating from basic science to the clinical setting. This consideration applies to both cardioprotection and to control of arrhythmias or pacemaking, but overall the first two strategies indeed stay on original, highly innovative targets and pathways. However, this threat must be taken into account, in particular for the effectiveness of Ca1.3 inhibition - in comparison to β-adrenoceptor or HCN blockade -, in preventing or limiting global remodeling in cardiac infarction.

For many aspects, the two team leaders run parallel programs with limited interactions.

- **Recommendations:**

The relevant relationship with companies should be exploited for moving toward application to H2020 collaborative projects and continue the experience with Marie Curie program. The team should pursue joint projects, both “intra-team” and with other IGF teams. In this regard, collaboration with teams E09 and E23 are welcome.

Team E13: Calcium channel dynamics and nociception

Name of team leader: Mr Emmanuel BOURINET

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	1	2
N3: Other permanent staff (without research duties)	0.5	0.5
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	1
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**4.5**	**3.5**

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

• Detailed assessments

Assessment of scientific quality and outputs

This is a small team as presently only the team leader holds a permanent position. Nevertheless, the team has produced 3 review articles and 3 major publications with participants to the team as first and last authors since 2008. Briefly, it validated T-type calcium channels encoded by the CaV3.2 as a target for treating visceral pain and identified the mechanism of CaV3.2 increased membrane expression in primary nociceptive afferent neurons innervating the gastro intestinal tract. (PNAS 2011). It developed a mouse model of chemotherapy induced neuropathy with oxaliplatin, the standard treatment of colorectal cancer (EMBO Mol Med 2011). It discovered a new peptidic pharmacological inhibitor of CaV3.2 channels (Patent CaV3.2 toxin - 2009), and characterized the analgesic properties of a new T-type channel small organic antagonist via blockade of the CaV3.2 isoform (Pain 2013). Beside, there are

also listed two publications in collaboration (J. Neuroscience, 2008 and 2009). The experts committee was informed of other very interesting submitted manuscripts during the presentation. The work relates to the engineering and detailed analysis of a genetically modified knock in mouse enabling tissue/cellular/subcellular distribution as well as conditional knock out of CaV3.2. Identification of CaV3.2 cellular/subcellular pattern in sensory neurons encompassing low threshold mechanoreceptor (in preparation). Analysis of C-fibers mediating pleasant touch and pathological pain with a specific genetic marker (in revision 2013)

Overall, the publications mainly relate to T-type channels and pain, and represent very significant contributions to the literature. This shows active collaborations of the team, while it remains focused on key goals.

Assessment of the team's academic reputation and appeal

The team leader is well recognized in the calcium channel field as an expert in T-type calcium channels in the pain pathway. The team leader received 8 invitations to international meetings, including FASEB summer conference, IUPHAR WorldPharma meeting, and Biophysical meeting symposium and will organize in 2014 the annual meeting of the French network on translational pain research. The team is a member of the Labex ICST (ion channel science and therapeutics) (2012-2020) and has several significant international collaborations, with leaders in the field in the development of transgenic animals and in pain. It attracted 4 post-doctorant (one foreign) and PhD fellows.

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

The team has established industrial contracts among which one through an ANR, and also a patent on a calcium channel toxin proposed to be developed by a pharmaceutical company.

Assessment of the team's involvement in training through research

Five theses were defended between 2008 and 2013, which is impressive, considering the small size of the team. All the students obtained their PhDs and have obtained a variety of positions. The team was also involved in a significant amount of training of Master's students.

Assessment of the strategy and the five-year plan

The team has presented an excellent and focused proposal on the role of T type channels in pain pathways. Very impressive preliminary results and collaborations were outlined during the presentation. Novel *in vivo* and *in vitro* techniques have been set up, for use in the future experiments (e.g. skin-nerve preparation, axonal conduction). The team proposes a set of inter-related projects that are highly likely to produce significant results which will be relevant to somatosensory processing and pain. New animal models are being generated and will be exploited to very good effect in the coming years. A permanent CR1 will join the team in 2014 and an additional PhD student has been recruited, this will increase the size of the team and make it possible to fully achieve the aims proposed.

Conclusion

Excellent team that produced very significant data on the role of T type channels in pain pathways. This group has the expertise, leadership, and motivation to successfully carry out the proposed experiments in the next five-year term. The experts committee was particularly positive about the originality of the project.

- **Strengths and opportunities:**

Very focused, good and relevant collaborations.

- **Weaknesses and threats:**

Small team, some of the expertise relies on a technician who will have to leave.

- **Recommendations:**

No specific recommendation. The team should aim at maintaining its current internationally competitive standard and possibly increasing group size.

Team E14: Calcium channels : structure-function and channelopathies

Name of team leader: Mr Philippe LORY

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	4	4
N3: Other permanent staff (without research duties)	1,50	1,50
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**7.5**	**5.5**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	2	
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	2	
Qualified research supervisors (with an HDR) or similar positions	2	2

• Detailed assessments

Assessment of scientific quality and outputs

This team currently has three permanent researchers. The team addresses the properties of voltage-gated calcium channels (Cav) and sodium leak channels (NALCN), their regulation and their involvement in physiology and pathophysiology, using various complementary strategies, from mass spectrometry to patch-clamp techniques.

The team leader co-signed several (>15) collaborative publications and reviews. Of the 5 major publications listed, the team leader was last author on one (J Neurosci, 2008), where the team showed that the the calcium channelopathy episodic ataxia type- mutants as well as a truncated form (D(I-II)) of the Ca(v)3.2 subunit of T-type calcium channel are misfolded, retained in the endoplasmic reticulum, and subject to proteasomal degradation.

In collaboration (J. Neurosci. 2009) the team (one member last author) showed that lipoamino acids are a family of endogenous T-type channel inhibitors, strongly inhibiting native Cav3.2 currents in sensory neurons with small effects on sodium and HVA calcium currents. They demonstrated that lipoamino acids produced thermal analgesia and that these effects were abolished in Cav3.2 knock-out mice.

A third member of the team was last author of an EMBO Reports, 2009 showing that the NALCN ion channel is activated by M3 muscarinic receptors in a pancreatic beta-cell line.

The overall standard of output was considered to be very good. Many of the other articles in collaboration have a broad ion channel theme. Some of the current projects described during the oral presentation have not yet come to fruition, but promise to have successful outputs and several papers are in preparation or submitted. For example, the investigation of a mouse model of cerebellar of ataxia

The experts committee was of the opinion that the three projects undertaken in the period under review, although all of a very good standard were rather independent, and did not appear to benefit from extensive synergy between team members.

Assessment of the team's academic reputation and appeal

The team leader is well recognised in the calcium channel field. He has been invited to 10 international meetings and is Chief Editor of "Frontiers in Pharmacology of ion channels and Channelopathies" and the team is part of the Labex ICST (Ion Channel Science and Technology 2012-2020). The team's expertise is broad, rather than being related to a specific aspect of channel function or dysfunction, although they have mainly concentrated on calcium channel involvement in ataxias and epilepsy. The team leader has been invited to a significant number of international meetings during the review period. One other member of the team has specific expertise in NALCN channels which are sodium leak channels.

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

Although there were industrial contacts, this has not been of significant importance to the group.

Assessment of the team's involvement in training through research

Three theses were defended between 2008 and 2013. Members of the team have also been involved in a significant amount of training of Master's students.

Assessment of the strategy and the five-year plan

One new senior team member with expertise in neurosecretion will join the team, and one team member has left in 2013, taking the project on calcium channel processing in cerebellar function and dysfunction. This will alter the balance and organization of the team, which will open new directions. The research strategy proposed was considered to be very good, although rather broad, with the aim to link NALCN and T-type channel function in the control of excitability. The physiological role of NALCN channels remains uncertain, and is one of the aspects to be addressed, as well as potential mechanisms of modulation of these channels via G protein coupled receptors and other interacting proteins. The phosphorylation of T-type channels is another aspect to be addressed.

The addition of the new team member will add a new dimension of expertise (neurophysiology and neuroendocrine secretion). The role of NaLCN particularly in chromaffin cell secretion will be investigated, in conjunction with the role of T-type channels.

Conclusion

The experts committee appreciated the work performed by this very good team but felt that their efforts might have been too much diluted and that complementarity between the members could have been more efficiently exploited.

- **Strengths and opportunities:**

The group is made up of four permanent members of staff, with complementary expertise.

- **Weaknesses and threats:**

The group needs additional funding to be able to recruit postdoctoral researchers and students to the team in the future. The team leader will become deputy director of the institute, and as such will have additional administrative roles in the future.

- **Recommendations:**

It is important that the focus of the group is maintained and it is hoped that the arrival of the new senior team member will positively contribute to this.

Team E15: Networks and rythms in endocrine glands

Name of team leader: Mr Patrice MOLLARD

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	2 (1)	1 (0,50)
N2: Permanent EPST or EPIC researchers and similar positions	6 (5,8)	5 (4,8)
N3: Other permanent staff (without research duties)	4 (3)	4 (3)
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	1
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**15 (12,8)**	**11 (9,3)**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	1	
Theses defended	4	
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	3	3

• Detailed assessments

Assessment of scientific quality and outputs

The objectives of the team converge toward a long-standing yet fundamental question in endocrinology: 'how is the production and release of peptide hormones controlled ?' This very innovative and original work has challenged key concepts in Endocrinology, such as the regulation of pituitary by hypothalamus and the "memory" of endocrine glands. Over the past 5 years, the team has demonstrated that many endocrine cell populations work as functional cell networks, which are essential for the amplitude and pulsatility of hormone release. The structure and functional responses of these networks were shown to adapt to external cues, and networks of pituitary cells were demonstrated to possess a form of long-lasting memory. The team also demonstrated the role of circadian clock genes (expressed in pituitary) in the regulation of growth hormone secretion, how peripheral hormones regulate pituitary functions though

specific hypothalamic neuronal populations (GHRH and TIDA), and the tight coupling of endocrine cell networks and microvasculature regulating the delivery of secretaguogues and nutrients. All these studies were performed with the help of state of the art *in vivo* imaging.

These results have been published in 12 original publications and 9 review articles with team members as first/last authors (including PNAS 4x, Nat Commun, J Neurosci and Endocrinology 3x), and 18 publications from collaborators in the last 5 years.

Assessment of the team's academic reputation and appeal

The members of the team were invited to 47 international meetings (including 24 abroad) and the team leader gave 4 plenary lectures. He organized two international meetings, is a member of the Executive Member Board of National Biophotonics Imaging Platform Ireland and a member of the Scientific Committee of Medical School of Montpellier. The group attracted 4 foreign postdoctoral fellows and a large number of visiting scientists for training reasons. The team has been awarded 7 ANR grants and one FP7 grant over the last 5 years, collaborative grants with NBIPI-HEA (Ireland) and a grant from the ANR-Investment for the Future program. The head of the team is a world leader in the field of *in vivo* imaging.

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

The team leader is scientific head of the *in vivo* imaging platform "IPAM" which is open to academic laboratories and to private companies. Other team members are scientific head of the IGF Animal Facility, member of the Animal Ethics Committee in Languedoc-Roussillon, vice-treasurer of the French Society for Chronobiology (SFC), and member of the organizing committee of the "Brain Awareness Week" at Montpellier since 2008.

Assessment of the team's organization and life

There are clear team objectives and the team has an excellent scientific environment with access to genomics, proteomics, imaging and screening platforms, as well as to an animal facility within the IGF. The team has been able to attract a large number of national and international scientists and has healthy relationship between group members. They run several groups and local meetings.

Assessment of the team's involvement in training through research

The team leader organized through IPAM two schools dedicated to "Small animal imaging" and he is a member of the FP7 Marie Curie "CEMP" Training program for 16 post-docs. 14 Master students were trained by team members. 4 graduate students defended their PhD, 3 started their PhD during the last 5 years. One team member received his habilitation to conduct research during this period.

Assessment of the strategy and the five-year plan

The group has a clear strategy for the next 5 years. Taking advantage of the data obtained and technological developments and using a variety of novel approaches, including optogenetics, transgenics and opto-rhythms, the group will address two main complementary topics:

1) How do parvocellular neurons and pituitary cell networks work in tandem to control basic body functions ?

2) What are the dynamics and role(s) of endocrine-vascular relationships ?

The first topic will involve the use of cre-lox-based optogenetic mouse models to identify activity patterns of hypothalamic and pituitary oscillators regulating GH and PRL ultradian rhythms in freely moving mice. Studies investigating the role of circadian clock genes will be pursued and potential defects of this system in hypopituitarism will be searched for. The second topic will use optogenetic tools to study the role of pericytes on the control of hormone pulse magnitude and oxygen supply *in vivo*. Some of the work is translational (hypopituitarism) and the topics are of great interest in endocrinology and expected to produce important results.

Conclusion

- **Strengths and opportunities:**

Excellent scientific team with an established international leadership in the field of regulation of endocrine functions.

- **Weaknesses and threats:**

None detected.

Team E16: Hormones, plasticité et stress

Name of team leader: Mr Freddy JEANNETEAU

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	1 (0,25)	1 (0,25)
N2: Permanent EPST or EPIC researchers and similar positions	3	3
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	2
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**7 (6.25)**	**7 (6.25)**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	3	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	4	4

• Detailed assessments

Assessment of scientific quality and outputs

The team that will be led by Freddy Jeanneteau is the result of the fusion of his group (Hormones, plasticity and stress) and the group formerly led by Gilles Guillon (Vasopressin, stress and depression). Whereas the first group determines how stress, and the release of glucocorticoids, affect brain functions, the members of the second group are interested in vasopressin receptor localization and its interaction with CRF receptors in the brain, in health and disease. Altogether, the scientific output is excellent. The two groups published, during the last 5 years, 24 original publications with team members as first/last authors, 4 review articles and 10 publications resulting from collaborations. Major publications as first/last authors include Nat Neurosci 2x, PNAS 2x, Nat Commun, Mol Cell Biol.

These originate about equally from both groups, but the publications by the present team leader result essentially from his post-doctoral stay in New York.

Assessment of the team's academic reputation and appeal

The members of the team were invited to 12 international and 6 national meetings. They organized the school of Electrophysiology in 2011 and 2012. The group hosted 2 visiting scientists. One team member is presently vice-director of the IGF and attracted an ANR and several other academic and industrial grants. The team leader got an ATIP-Avenir grant.

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

The team held industrial contracts with a pharmaceutical company (2009-2012) and Brahms (2012). It got exposure in press, radio and science festivals.

Assessment of the team's involvement in training through research

One team scientist is member of the scientific council (2008-2012) and director of the CBS2 Doctoral School, and president of the Patch-club of Montpellier. The group has contributed to the training of several Master students. Team members are teaching at the École des Infirmiers-Anesthésistes of Montpellier, and have various academic responsibilities.

Assessment of the strategy and the five-year plan

Both groups resulting from the fusion will continue their own program with relatively little interaction. The team leader intends to pursue its ongoing research programs with the aim of better understanding the role of BDNF on glucocorticoid-mediated plasticity and the function of peptide receptors (VP, OT, CRF) in healthy and diseased brain. The project is clearly described and timely. It approaches important questions in the field, and the group has the necessary expertise to contribute much to the progress in these areas. The project of the other group was described in the written document but not exposed during the presentation. It will consist in the continuation of recent activities, with the characterization of CRH and AVP receptor dimers as a unique signaling unit in the brain, with the help of knock-in mouse models expressing receptors tagged with fluorescent proteins. Despite the recent productivity resulting from this activity, it was felt that there is no obvious leadership for this topic beyond the departure of the present group leader. As the proposed leader of the fused team has clearly no plans to direct this research activity, it is likely that this second topic will wane and disappear in the near future.

Conclusion

- **Strengths and opportunities:**

Merging two groups should have added strength to the team and should open opportunities for common questions and projects.

The new team leader has an excellent publication record from his post-doctoral fellow and a solid research program. He is therefore expected to pursue at the same level.

- **Weaknesses and threats:**

From the presentation at the interview and the written documentation, the merge of the two teams appears “forced” and not a fusion based on common scientific interests. This may be due to the imminent retirement of the former leader and other members of one group and the uncertainty regarding the continuation of its research projects, despite its excellent recent scientific output.

- **Recommendations:**

Integration of the two groups should be achieved progressively, and a more united appeareance of the team should be presented to the outside world.

Team E17: Signalling, plasticity and cancer

Name of team leader: Ms Julie PANNEQUIN

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	6 (2,50)	4 (1,75)
N2: Permanent EPST or EPIC researchers and similar positions	4	5
N3: Other permanent staff (without research duties)	1 (0,50)	1 (0,50)
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	5	1
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**16 (12)**	**11 (8.25)**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	5	
Theses defended	2	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	6	6

• Detailed assessments

Assessment of scientific quality and outputs

The team was composed in the past years of 5 full-time scientists, 5 professors and assistant professors and 2 technicians. The aim of the team during the past five years was to decipher the mechanisms involved in colorectal tumorigenesis. The team has developed three major research axes focusing respectively on tight junction and scaffolding proteins, nuclear receptors, and progastrin as a target for clinical management of patients with colorectal cancer. The progastrin project has mobilized resources and manpower in order to create and later expand a spin-off company with the aim of developing neutralizing antibodies against progastrin as a new therapeutic strategy in colon cancer. This activity has limited the number of publications (1 in Cancer Res 2010) due to intellectual property issues, but has successfully led to 5 patent applications and increased the company staff to 17 persons, which *in fine* was

bought in 2011 by a major French Pharmaceutical Company. The results obtained by team members working on other projects gave new insights on colorectal cancer development especially:

(1) on the role of Tcf-4 maintaining low levels of claudin-7 via Sox9 at the bottom of the colonic crypts and the impact of simplekin on differentiation and tumorigenicity by up-regulating claudin-2;

(2) on the impact of ¤-arrestin2 on colorectal tumorigenesis;

(3) on the important role of PXR in regulating xenobiotic metabolism and disposition in liver and in cancer cell resistance towards chemotherapeutics.

The team's production is a fine balance between fundamental research and clinical and technological transfer.

The scientific production of the team is of high levels both quantitatively and qualitatively, with 11 original publications with team members as first/last authors (among which PNAS 2x, Cancer Res 2x, Gastroenterology), 22 original publications from collaborative work and 5 reviews. However, part of this production involves the two former team leaders who have recently left the team for different reasons, and the production of the present team leader was only 6 publications in the past 5 years with only one (Cancer Res) as first author and none as last author. Team results were published in excellent journals (4 with IF > 10, 13 with IF between 5 and 10) covering multiple science fields.

Assessment of the team's academic reputation and appeal

The team has an excellent academic reputation and appeal. One researcher joined the team in 2010. One post-doctoral fellow from the team has successfully competed for a permanent position as a CR1 at INSERM in 2013. Team members were invited for oral presentations in 9 national and international meetings and for 20 seminars, acted as reviewers for high impact journals, and were invited to write reviews and book chapters. One staff scientist was a member of the Cancéropole Grand Sud Ouest committee.

The team has recently joined the Epigenmed LabEx and members of team are principal investigators and coordinators of multiple projects funded by national agencies (2 ANR, 2 INCA, Cancéropôle Émergence) and patient associations (Ligue contre le cancer, 5 ARC).

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

The creation and expansion of a very successful Spin-off company was an exceptional achievement of the team in the social and economic environment. Members of the team have also established collaborations with different French pharmaceutical companies. The team has also filed 5 patents.

Assessment of the team's involvement in training through research

During the past 5 years, 3 theses have been defended and 3 HDR have been obtained. Four members of the team have teaching responsibilities at Université Montpellier 1. One member is in charge at the local level of a teaching axis within M1-Master Pro Biology of Health (Université Montpellier 1) and at international levels with M1 teaching programs at SFAX University (Tunisia) and University of Casablanca (Morocco). There are presently 6 HDR supervising 5 PhD students and 6 Master students.

Assessment of the strategy and the five-year plan

The scientific project is a direct extension of the work carried out by the team during the past four years, with the aim of understanding the molecular mechanisms involved in colon cancer progression. Following the departure of two full time scientists (former team leaders), the new team leader has focused the project on the role of two molecules, progastrin and PXR, and upon one specific pathological situation that is cancer recurrence as a result of resistance to chemotherapies. The project will be based on manipulated cell lines overexpressing PG or PXR that will be evaluated using "Omics" technologies (microarrays, translatome, phosphokinome) and subsequent challenges of identified candidates in subcutaneous xenograft and orthotopic animal models. Circulating tumor cells will be tracked, isolated and cultured *in vitro* in order to evaluate the tumor initiating cell phenotype. Additionally, one particularly arduous challenge of the project will be to analyze the behavior of transplanted colorectal cancer patient samples into mice. Such part of the project will be possible thanks to collaborations developed locally with

Montpellier's hospital and because the team is a member of the newly granted Site de Recherche Intégrée sur le Cancer of Montpellier (SIRIC).

The project is feasible in term of scientific expertise, ambitious with potentially high impact on CRC management. It must be emphasized that the team possess the necessary combination of expertise to carry on a highly successful project.

Conclusion

- **Strengths and opportunities:**

The team has proven high levels of expertise on PG and PXR. The objectives of the project are well defined with a "bench to bedside" strategy. Access to IGF facilities and outstanding equipment is highly valuable to the project.

- **Weaknesses and threats:**

A weakness of the project is the absence of known molecular mechanisms explaining the activities of progastrin on colon cancer cells. The identification of the molecular target (receptor ?) of progastrin does not appear to constitute a major aspect in the scientific strategy. This might impact the significance of the results obtained and the ability to publish them in the best journals.

The existence of links and collaborations with other teams of the IGF working in the same area (colon cancer) was not described in the project. Also, potential national or international collaborations were not mentioned in the strategy of the team. Isolation of the team may be detrimental to the project in a highly competitive field.

- **Recommendations:**

The team should develop a research axis dedicated to the better understanding of the molecular mechanisms involved in progastrin actions, allowing publication of team's findings in high profile journals. Considering deeper interactions and collaborations with other teams involved in similar topics within the IGF and outside might also be valuable. The international visibility of the present team leader could also be improved.

Team E18: Self-Renewal and differentiation of epithelia

Name of team leader: Mr Philippe JAY

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	3	4
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	1
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**6**	**5**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	4	
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	2	3

• Detailed assessments

Assessment of scientific quality and outputs

The aim of the team was to understand the processes that maintain homeostasis of intestinal epithelium and characterize the mechanisms responsible for the rupture of this homeostasis leading to chronic inflammation and cancer. The team has developed three research axes, based on the development and use of transgenic and conditionally gene-deficient mouse models:

(1) Thanks to its expertise on the role of Sox9 in the intestinal epithelium, the team has determined with another IGF team the role of Tcf-4 in the maintenance of low levels of claudin-7 via Sox9 at the bottom of the colonic crypts. The team has also generated animals with tissue-specific deletion of Sox9 in Paneth cells by generating

Sox9$^{LoxP/LoxP}$ animals that were bred with Villin-Cre^{ERT2} mice. Interesting, preliminary results were obtained showing that Sox9 expression is necessary for maintaining the phenotypic identity of Paneth cells but not their survival.

(2) By combining experimental approaches on mice and mathematical modeling, the team demonstrated the absence of asymmetric strand segregation in intestinal stem cells and that these cells must rely on other mechanisms to maintain the integrity of their genome.

(3) A major achievement of the team is the characterization of tuft cells, a fifth intestinal epithelial cell type, and the identification of markers for these cells (Sox9, Dclk1, Cox1, Cox2, Hpgds). This work allowed demonstrating that epithelial Dclk1-expressing cells are not intestinal stem cells, as previously proposed, but tuft cells, and that these cells originate from LGR5^{+} stem cells.

The scientific production of the team is of high level, both quantitatively and qualitatively, with 6 original publications with team members as first/last author (among which 4 in top journals in their fields: J Cell Biol, Oncogene, Gastroenterology, Nat Commun), 6 original publications as co-authors, 3 reviews and two letters to the editor.

Assessment of the team's academic reputation and appeal

The team has an excellent academic reputation and appeal as one post-doctoral fellow of the team has successfully competed for a permanent position as a CR2 at CNRS. The leader of the team is the current coordinator of the GIStem (consortium of five laboratories over France), is a member of multiple French and European evaluation committees (INCA, Marie Curie Actions COFUND grant) and is also a member of scientific committee of the National Ligue Contre le Cancer. The team leader is regular reviewer for several high profile journals (Nature Genet, J Exp Med…). Team members were invited to 4 national or international meetings, and 7 seminars over the past 5 years.

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

The leader of the team shares the responsibility of coordinating the colorectal cancer programs of the newly created integrated cancer research site (SIRIC) in Montpellier. The leader of the team was for several years a consultant (scientific strategy) of a spin-off company. Two grants (ARC) were obtained with companies as partners. The team leader is co-inventor of a patent. He has attracted regular funding, as coordinator of an ANR and two INCA projects, and as partner of two INCA and an ERC grants.

Assessment of the team's involvement in training through research

The involvement in training is very good for the small size of the team. During the past 5 years, 2 PhD theses have been defended and one HDR was obtained, while 4 PhD students have been recruited. The current number of HDR (2) is however limited for the supervision of the ongoing 4 theses.

Assessment of the strategy and the five-year plan

The scientific project is in direct line with the recent past activity of the team. The project is based on the development of a series of conditional knock out animals with specific deletion of target genes in stem cells, Paneth cells (VillinCre^{ERT2}) or Tuft cells (Dclk1-Cre^{ERT2}). It has three objectives:

(1) Determining the function of Sox9 in healthy and cancerous intestinal epithelium. The role of Sox9 in Paneth and in stem/progenitor cells in the initiation and progression of intestinal tumors will be analyzed by using (Sox9$^{LoxP/LoxP}$; Apc$^{LoxP/+}$; VillinCre^{ERT2})-animals. Transcriptomic analyses will be carried out on Sox9-deficient and Sox9-proficient tumors. In a non-malignant context, gene expression profiles of the intestinal crypts will be determined using (Sox9$^{LoxP/LoxP}$; AhCre) and (Sox9$^{LoxP/LoxP}$; VillinCre^{ERT2}) animals. The impact of Sox9 deletion in the Tuft cells on the intestinal epithelium phenotype will be characterized by crossing Sox9$^{LoxP/LoxP}$ with Dclk1-Cre^{ERT2} animals.

(2) The role of Tuft cells in normal and pathological situations (infection, colitis, tumorigenesis) will be characterized by using in Dclk1-Cre^{ERT2} animals and Floxed animals for identified transcription factors.

(3) The project is also aimed at identifying genetic and epigenetic determinants of susceptibility to tumorigenesis based on the observation that Apc mutation leads to two distinct groups of animals with low (1-20) or high (40-120) tumor multiplicity.

The project is very original, based on highly relevant genetic animal models, most of which have already been generated.

Conclusion

- **Strengths and opportunities:**

The project is based on solid recent and original data generated by the team. It is ambitious with both high cognitive and potential impacts on CRC management. Access to IGF facilities and outstanding equipment is highly valuable to the project. The team has established an excellent network of external collaborations.

- **Weaknesses and threats:**

The team is relatively small and is not surrounded by many groups sharing a common interest in cancer and stem cells. The team leader considers however that the benefits resulting from the exceptional environment of the IGF in terms of know-how and efficient platforms compensates largely this limitation.

The field of intestinal stem cells and their role in tumorigenesis is very active and highly competitive. Provided its background and available genetic tools, this team can likely cope with this competition.

Attention should be given to the number of HDRs in the team.

- **Recommendations:**

A better integration of the activities of this team with those of the other IGF group involved in colon cancer research would be beneficial to both teams. The international visibility of the team through invited participation to international meetings abroad should be improved.

Team E20: Neural circuits and signal transduction

Name of team leader: Mr Emmanuel VALJENT

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	1	1
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	4	1
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**5**	**2**

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

• Detailed assessments

Assessment of scientific quality and outputs

The team has been at the IGF only since 2010. The team has been very productive, contributing to a number of projects related to striatal anatomy and physiology and to the distribution of dopaminergic inputs to striatum and hippocampus. During the evaluation period, the team leader has been an author or co-author in 30 publications, including papers in Nature, Sci Signal, Biol Psychiatry, J Neurosci, PNAS. In 6 articles, team members are the 1st or the last author. Among the 6 published reviews, the team leader is the first author in a TINS publication. The number of articles and the level of journals is impressive for a small team, but the number of papers directly from the lab is smaller. While at IGF as an ATIP-Avenir team, the team has contributed to 3 interesting projects that lay the foundation for the future research at the IGF.

Assessment of the team's academic reputation and appeal

The team is still in the early phase of adjusting to IGF, but has alreay been internationally recognized by 3 invitations to international meetings, 8 seminars and review invitations (incl. TINS). The team has attracted 3 foreign postdocs and a scientific visitor. The team is a member of the Labex EpiGenMed and was involved in the organization of the first IGF colloquium. The team has received a Marie-Curie grant but it would be important to get more involved in European funding programs.

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

The group has an industrial contract with Sanofi-Aventis and has participated in the Brain Awarness Week activities. This is very good, given the short time at the IGF.

Assessment of the team's involvement in training through research

3 international postdoctoral fellows, 1 graduate student, 6 master students. Participation in the Master Biomed program.

Assessment of the strategy and the five-year plan

The general objective of the team is to carry on the identification of the molecular and cellular mechanisms involved in dopamine-controlled learning and study its alterations in neurological and psychiatric disorders.

The plan involves 4 major projects:

(1) gain new insights into the anatomo-functional organization of the striatum, the hypothesis tested being that information processing in this striatal area could be entirely based on D1R-expressing medium-sized spiny neurons;

(2) identify the mechanism through which dopamine D2 receptor-expressing neurons of the extended amygdala control generalization of anxiety and fear;

(3) test whether local mRNA translation could be an important process that elicits the neuronal plasticity in the context of drug addiction and L-DOPA-induced dyskinesia;

(4) specifically identify, at the cell level, mRNAs translated in the striatum.

All these project involve a lot of originality and imaginative approaches and the plan certainly does not show any lack of ambition or risk-taking. Most of the proposed projects are based on original findings of the laboratory, which greatly increases credibility and feasibility. Proposed projects involve international collaboration with leading laboratories working on striatum. Striatum is becoming the clear niche for the team which should concentrate on that. On the other hand, for a small laboratory this plan sounds too ambitious. It might have been better to focus on a fewer projects and this is apparently what the team is planning to do. Nevertheless, these projects will widen the experimental repertoire of IGF groups and the team will be a valuable collaborator for several other groups in the institute and surrounding in the future.

Conclusion

This is a young group that is taking off and bring important expertise to the IGF. The team has a small size but intensive collaborations with external teams and a very good visibility. The work program is rich and creative. A very effective strategy is needed to bring their findings at a functional and physiologically relevant level.

- **Strengths and opportunities:**

- active collaborations, with excellent publication record stemming from these collaborations;

- several interesting original findings form a basis for future studies;

- good niche in striatal studies;

- new team in the IGF, but already well adapted;

- opening of the animal house will be critical for the team;

- active collaborations both internationally and locally.

- **Weaknesses and threats:**

- over-ambitious 5-year plan;

- relatively few papers coming out of the group itself;

- participation in international and European grants.

- **Recommendations:**

The group has recently started at the IGF and has opened an active research program in the area that had not been at the core of the institute before, including behavioral testing. Within the time at the institute, the group has found a new anatomical organization within striatum that team members are now investigating at functional level. The experts committee felt that the findings in striatal organization are very promising and interesting, but that it will be very important to bring these findings at the functional and physiologically relevant level. The group has been very active at collaboration with leading groups in striatal structure and function, but the scientific output from the group itself is not as good as those through collaborations. In the coming years, it will be important to focus on the productivity of the group and on securing steady funding. Focusing on the core competence of the group in the striatal system will help in this effort.

Team E21: Cell Cycle Clock Genomics (C3G)

Name of team leader: Mr Frédéric BIENVENU

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	1	1
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**3**	**1**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students		
Theses defended		
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions		

• Detailed assessments

Assessment of scientific quality and outputs

This junior team was created in 2011 and is supported mainly by an AVENIR/ATIP program as well as a Mérieux research grant. It is a relatively small team with the team leader as sole full time scientist, 3 post-doctoral fellows and one technician. The team leader has one major publication (in Nature, 2010) as first author, and two other publications as co-author (in Nature and Dev Cell), all resulting from his post-doctoral stay at Harvard University. No publication has so far arisen from the work performed in IGF. The team's work focuses on the mechanisms of transcriptional regulation by cyclin D1 and its implication in cell survival and proliferation using both animal models and cell cultures. The aim of the team is to understand the role of cyclin D1 in cancer progression and to discover new inhibitors of its functions. Several technological developments were necessary to undertake this project especially the

screening of siRNA/RNA/protein complexes. A patent application has resulted from this work. This is thus a very original scope of research which required several theoretical and methodological breakthroughs. Results are too briefly described and in the absence of publications, it is difficult to evaluate the impact of the research performed since the recent creation of the team.

Assessment of the team's academic reputation and appeal

The team leader has published in the past in the best journals (Nature, Dev Cell…) but it seems too soon to evaluate his academic impact. However, he has been able to attract three good post-doctoral fellows and he is a specialist of cyclin D1 since his first steps in research. The team has attracted a significant number of grants allowing to fund its research and hire post-doctoral fellows and a technician.

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

The team is implicated in the Labex EpiGenMed and has already several patents filed, or in preparation, on both technological transfer and theranostics. The team has established collaboration with the local company Medesis Pharma.

Assessment of the team's involvement in training through research

The team has so far no PhD student but was involved in the training of undergraduate and graduate students.

Assessment of the strategy and the five-year plan

The scientific project is a continuation of the ongoing activities with the aim of publishing in high impact journals, which is commendable. The scientific strategy is divided in short term plan - publication of available results regarding gene targeting by siRNA, and the opportunity to target cyclin D1 in cancer and Parkinson disease - and medium term plan, with the aim of determining the mechanism of recruitment of cyclin D1 to the genome and its influence on transcription of other targets, drug resistance and epigenetics. The transcriptional impact of cyclin D1 will be investigated in cancer (stem) cells, dopaminergic neurons, cerebellum development, mammary gland development and in the process of epithelial-mesenchymal transition and migration of neural crest cells. In the longer term, studying the role of D-type cyclins will be extended to organ homeostasis with particular emphasis on brain architecture and plasticity, liver regeneration, pancreatic integrity and fertility. All these studies will be performed in collaboration with local and international groups. However, the written proposal is too short to make a thorough evaluation (only title of individual programs are provided) and the oral presentation did not really clarify on what the team is really going to focus.

Conclusion

- **Strengths and opportunities:**

The project is based on previous data obtained by the team leader during his post-doctoral stay. Several patents should be obtained in the future. The project has high potential cognitive impacts and could be clinically relevant to both cancer and neurodegenerative diseases.

- **Weaknesses and threats:**

The project is extremely broad and ambitious (although very poorly described) especially as the team leader is still very young and the team rather small. Thus the team should either consider hiring more scientists to increase its work force, or target precisely fewer points.

- **Recommendations:**

The scientific program appears to require maturation, and should focus on a limited number of specific aspects. The team should also plan to investigate more deeply some of their hypotheses within the group, and not only through collaborations. May be, this team could benefit from direct mentoring from a more senior scientist sharing complementary interests both at scientific and technological levels.

Team E22: Determinants and Correction of Insulin Secretion Loss in Diabetes

Name of team leader: Mr Eric RENARD

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	4 (0,25)	4 (0,25)
N2: Permanent EPST or EPIC researchers and similar positions		
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)		
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**5 (1.25)**	**5 (1.25)**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	2	
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	4	4

• Detailed assessments

Assessment of scientific quality and outputs

The overall production of the team is impressive, with 56 original publications, 32 reviews and 3 book chapters over the last 5-year period. This production is highly collaborative. 23 original publications were published with team members as (co-first/(co)last author, among which 4 in excellent journals with impact factors > 7 (3 x Diabetes care, 1 x Diabetes). However, the relatively limited number of high standard publications originating directly from the team should be balanced by the nature of the research, i.e. applied research close to patients. The numerous papers published through collaborations highlight the strong reputation of the team having valuable expertise in artificial pancreas and closed loop monitoring of glycemia in diabetic patients.

Assessment of the team's academic reputation and appeal

The team has acquired a strong reputation regarding the development of artificial pancreas, and plays a key role in the progressive improvement and testing of devices within international networks. This reputation is illustrated by the numerous collaborative papers. There were 33 invitations of team members to national or international meetings (25 held abroad) and 43 invitations to seminars. The team was a partner of 3 FP7 programs, and obtained 5 grants from the international charity organization JDRF. It also attracted 3 foreign post-docs during the period.

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

Being patient-oriented, the team has regular interactions outside of the academy. A strong added value is the therapeutic education of diabetic patients. The team has many contacts with companies (Sanofi, Novo-Nordisk, Roche Diagnostics, Medtronic), partly through the EU-funded networks.

Assessment of the team's involvement in training through research

No PhD graduated over the last 5 years. However, the team joined the unit recently (2013) and now 2 doctoral students are enrolled. So, this new affiliation should improve academic training.

Assessment of the strategy and the five-year plan

The research plan is a follow-up of previous projects towards improvement of artificial pancreas devices and diabetes management. By essence, this will translate into baby steps with modest but valuable outcomes each year. The team has a solid international network of collaborators (USA, United Kingdom, Sweden, Italy…).

Conclusion

- **Strengths and opportunities:**

Highly valuable translational medicine, reinforced by the new affiliation to the unit. The past achievements of the team and the existence of an excellent network of collaborators should warrant success in the improvement of artificial pancreas.

This new team with a strong connection with hospitals and patients will be an asset for translational activities of all other IGF teams.

- **Weaknesses and threats:**

A relatively low fraction of the publications with team members as first/last authors appeared in high profile journals, as compared to the collaborative output.

- **Recommendations:**

The team should enhance its interaction with basic research and its collaborations with other IGF teams. This could be achieved partly through the newly established collaboration with team E08.

Increase the average level of publications originating directly from the team.

Team E23: Molecular mechanisms of regeneration

Name of team leader: Mr Chris JOPLING

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		1 (0,50)
N2: Permanent EPST or EPIC researchers and similar positions	1	1
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**4**	**2 (1.5)**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	1	
Theses defended		
Postdoctoral students having spent at least 12 months in the unit	2	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions		

• Detailed assessments

Assessment of scientific quality and outputs

The team leader has joined the IGF in 2012 to set up his laboratory and establish his research program after completing a very successful postdoctoral training at the Salk Institute. He made outstanding contributions to the understanding of heart regeneration in zebrafish. In a seminal Nature publication as first author, he described that heart regeneration in zebrafish is based on the proliferation of existing cardiomyocytes, which partially dedifferentiate and initiate proliferation upon myocardial damage. Despite a relatively short time in Montpellier, the team already achieved a remarkable scientific output at the IGF. They demonstrated that activation of the p38-MAPK pathway blocks proliferation of zebrafish cardiomyocytes, therefore preventing regeneration. Another important discovery was the finding that hypoxia induces dedifferentiation of zebrafish cardiomyocytes, which might have

impact on our understanding of mammalian heart regeneration. During the course of these experiments, they identified several genes that are differentially regulated during zebrafish heart regeneration, which will enable the role of these genes for cardiac regeneration to be studied in more detail. These experiments were published in Circulation and Cell Cycle. The team has established a new culture system for adult zebrafish cardiomyocytes, which provides an attractive screening system to identify genes (and compounds) that regulate heart regeneration and cardiomyocytes proliferation. The manuscript is currently under revision in Nat Protocols.

The team has also embarked on a new project to study the role of mechanosensitive ion channels (i.e. piezo1), which are involved in touch sensing and regulation of erythrocyte volume. Although not directly linked to the main research line, analysis of mechanosensing is a highly innovative and promising field, which already resulted in a publication in J Neurosci.

In summary, the research projects initiated and completed by this new team are highly innovative and groundbreaking, giving rise to the highest expectations. The team's research is -by nature- interdisciplinary, linking physiology and developmental biology to molecular biology and translational medicine. New experimental techniques have been established, which enable the latest pharmacological screening approaches to be applied to zebrafish biology and heart regeneration.

Assessment of the team's academic reputation and appeal

Within the academic community, the team leader has gained a lot of attention and established himself as a respected researcher. Although still a relatively junior researcher, he has been invited to several important meetings.

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

Collaborations and specific interactions with the social, economic and cultural environment are currently not really visible, which at the moment should also not be a priority. Joint productions with non-academic partners make only sense when promising results are available, which can be readily exploited. Nevertheless, the formulated ideas about reprograming of mammalian cardiomyocytes to enable mammalian heart regeneration and cardiomyocyte proliferation have potentially a strong translational impact.

Assessment of the team's organization and life

The relatively small team has three postdoctoral fellows and a PhD student. Several projects rely on technical expertise provided by specialized services. The proposed research plan takes advantage of the available resources at the IGF and seems organized in an excellent manner optimally exploiting local resources. As mentioned above, the team leader is a relatively recent arrival at the IGF and hence had only very limited time to build up new collaborations and networks in France and in Montpellier. Nevertheless, it is evident that close ties with other research groups working on the heart have been established. Namely, the team collaborates with the E12 team to apply findings the zebrafish work to mammalian systems and human beings. Specific plans are also provided how to extend the research to the translational arena. The proposed projects utilize interdisciplinary approaches and represent a good balance of high-risk and more down-to-the-earth experiments.

Assessment of the team's involvement in training through research

The team currently trains one PhD student and three postdoctoral fellows, which is the perfect size for a young research group, leaving space for further expansion. Training of the student and fellows in the lab is in a highly attractive area, which will facilitate career progress and enable the fellows to compete successfully on the job market.

Assessment of the strategy and the five-year plan

Three different major research lines are proposed:

(I) genetic regulation of myocardial regeneration;

(II) cardiomyocyte hypertrophy versus proliferation;

(III) adult mammalian cardiomyocyte reprograming.

Two of the three research lines capitalize on previous expertise in zebrafish biology while the third line moves into the arena of mammalian cardiac biology and regeneration.

(I) Specifically, the team proposes to further delineate the signaling pathways regulating zebrafish cardiomyocyte proliferation and heart regeneration. They have already identified a number of potentially interesting molecules which they now want to study in more detail using the highly advanced tool box of zebrafish genetics. Target genes include NFκB, p38 MAPK, JNK, but also Pim1, S100A, Trithorax, Sprouty4, ATF3, Caveolin1, Tal1, GATA1 and SRF. Some of these molecules have already been studied in the context of heart regeneration in mammals. Mechanical signals play a pivotal role in the regulation of the cardiovascular system but relatively little is known about the molecular machinery that senses and transmits mechanical signals. The current studies on piezo1 performed by the team provide an excellent basis to further study this unexplored territory.

(II) In the second line of research, the team proposes that some of the genes, which induce hypertrophy in adult mammalian hearts, might induce proliferation of zebrafish cardiomyocytes. The idea is that specific conditions in adult mammalian hearts render pro-proliferative signals hypertrophic. Comparison of mammalian and zebrafish hearts subjected to the same stimulus (i.e. overexpression of the same gene) might reveal why mammalians hearts react differently compared to fish hearts. The team wants to overexpress βAR, AGTR1 and gp130 in zebrafish hearts and study downstream effect in fish cardiomyoctes to pursue this task.

(III) In the third research line, the team proposes a screening project to identify factors that might induce a dedifferentiated state in cardiomyocytes enabling them to respond to pro-proliferative cues. Although the design of the screening makes sense, this project is certainly the one with the highest risk of failure. Several attempts have been made in the past to induce proliferation of cardiomyocytes and none was particularly successful. However, in a recent publication, it was claimed that certain miRNAs might promote proliferation of newborn and even adult cardiomyocytes, although these experiments have not been repeated by other groups so far. Hence, it might make sense to include miRNAs in the screening efforts. There are also doubts that identification of factors that enable proliferation of newborn cardiomyocytes will have effects on postmitotic mammalian cardiomyocytes, in particular binucleated cardiomyocytes. It might be a good idea to distinguish between mono- and binucleated cardiomyocytes.

In summary, the proposed research plan is realistic and has a good chance of success within a 5-year period. The research strategy is highly innovative, takes advantage of several innovative methods and is interdisciplinary, integrating ideas and approaches coming from physiology, cell biology, developmental biology, drug screening and molecular biology.

Conclusion

- **Strengths and opportunities:**

The past accomplishments of this newly recruited team, partly before its arrival in IGF, are outstanding. This is an excellent recruitment for the institute.

The team takes advantage of the zebrafish as a highly-efficient regenerative species using advanced zebrafish genetics. The use of zebrafish as a model system to study heart regeneration is a major strength providing major opportunities. As a model system, the zebrafish is highly approachable allowing experiments that are difficult or even impossible to do in mammals. The research program is focused and provides an excellent balance between high, medium and low risk experiments.

- **Weaknesses and threats:**

At present it is relatively unclear whether results obtained for zebrafish heart regeneration are relevant for mammalian myocardial regeneration. The zebrafish physiology (low blood pressure, lack of coronary vessels, lack of compacted myocardial layer, cold-blooded animal) is rather different from mammals, which makes a direct comparison difficult. Hence, it is possible that we will learn a lot about zebrafish heart regeneration but end up with the finding that the involved mechanisms are less relevant for mammals and humans. It is clear, however, that this question cannot be answered at the moment and proper experiments have to be done to come up with definitive answers.

Several of the genes that are listed in the research plan have already been studied intensively in mammals. There is a certain danger that upcoming results will reproduce findings already made in mammals, which would be a bit disappointing.

Despite the great opportunities that the zebrafish provides in terms of a genetic model organisms, which is highly approachable for all kinds of imaging techniques, there are also severe limitations, foremost the lack of reagents (antibodies) and physiological techniques. For example it is difficult to assess function of the heart (pump efficiency, contractile force, etc.) in zebrafish.

Finally, there is as a strong international competition in the field of cardiac regeneration (including in zebrafish). For a young group with limited resources, it might be difficult to meet such challenges.

- **Recommendations:**

At present, the team is in an exploratory phase and has to identify the most promising subtopics. Once this is accomplished, it might focus its resources on the most rewarding project. It seems also imperative to establish productive collaborations with other research teams, both on-site and abroad. The screen for new factors that might allow reprogramming of adult cardiomyocytes is relatively risky but also highly rewarding. The team leader might seek collaborators, which might help him with screening of small compounds and miRNAs. Finally, it seems prudent to focus on genes that have not already been studied extensively in mammals.

This team needs help for the maintenance of its zebrafish lines.

Team E24: Structural studies of G protein coupled receptors : focus on class C

Name of team leader: Mr Guillaume LEBON

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions		
N2: Permanent EPST or EPIC researchers and similar positions	1	2
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	2	1
N6: Other contractual staff (without research duties)		
TOTAL N1 to N6	**3**	**3**

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

• Detailed assessments

Assessment of scientific quality and outputs

This is a newly-established team (January 2013) in the Institute focusing on the structure of class C GPCRs. The team leader has strong expertise in structure-function studies of receptors, membrane protein biochemistry and X-ray crystallography. The team leader was directly involved in the rapidly expanding field of GPCR structure determination by providing the first high-resolution structure of an agonist-bound adenosine A2A receptor. This provided important novel information about GPCR structure and mechanisms, opening new avenues for future basic research and pharmacological applications. The publication record in recent years is excellent with several 1st author publications: Nature 2012, J Mol Biol 2011 and Mol Pharmacol 2009. The team and group leader also contributed two review articles in high impact journals: Curr Op Struct Biol (2012, 1st author), Nature 2013 (3/6).

Assessment of the team's academic reputation and appeal

This is a small team currently composed of three members (team leader, 1 CR2 researcher and 1 research assistant). The CR2 researcher who has just been appointed at INSERM was a former postdoctoral fellow in the team, testifying of the excellent scientific quality of the group. The team leader has a strong reputation in the field of GPCR structure and good international visibility. In recent years, he had several (5) invitations to international symposia or conferences, and gave several invited seminars in France and overseas. He also organized a Gordon Research Seminar on Molecular Pharmacology dedicated to young scientists. The team initiated a collaboration with a team at the nearby Institute 'Centre de Biochimie Structurale'. The team is well funded, in particular by obtaining the prestigious ATIP-Avenir label (2013-2015). In conclusion, this is a highly promising team, working on an important and timely topic with strong translational potential.

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

The team leader is co-inventor on two patents and has regular contacts with industry. In particular, the X-ray structure determination of A2A receptors was developed in collaboration with a british pharmaceutical company. A collaborative contract with the company Actelion has also recently been signed. This activity is excellent.

Assessment of the team's involvement in training through research

Not applicable (team just arrived in the institute).

Assessment of the strategy and the five-year plan

The project aims at solving the structure of several class C GPCRs (mGluRs, GABA-B receptors) using X-ray crystallography and single-particle cryo-EM imaging. The structural studies will focus both on drug-receptor interactions and receptor-signaling molecule complexes. The objectives are well-thought out and contain highly original and innovative aspects (use of 3D-DNA origami nanostructures). Overall, this is an excellent project that should provide novel important information and concepts about key signaling receptors.

Conclusion

Very promising junior team, highly motivated. The experts committee stressed the originality and existence of cutting edge projects.

- **Strengths and opportunities:**

An excellent project on a highly relevant and timely topic. The combination of X-ray crystallography with cryo-EM approaches is expected to yield critical novel information about GPCR structure and dynamics. The team brings novel expertise in the Institute and makes a great addition to the current topics by installing a new structural biology axis. Moreover, the expertise and possibilities for collaboration provided by other teams at the IGF and in nearby institutes are expected to be a major boost for the project implementation

- **Weaknesses and threats:**

Given the high level of competition in the field, the team should increase its workforce.

- **Recommendations:**

The team has currently limited human resources, so increase of the critical mass by hiring new postdoctoral fellows and PhD students or technicians should be considered as the top priority. In order to gain full independence for student supervision, the experts committee also recommends the team leader to defend as soon as possible his Habilitation à Diriger des Recherches (HDR). Finally, it is also recommended that the team applies to the most competitive international calls.

5 • Conduct of visit

Visit dates:

Start: January 22nd 2014, 12.00 pm

End: January 24th 2014, 06.00 pm

Visit site:

Institution: Institute of Functional Genomic

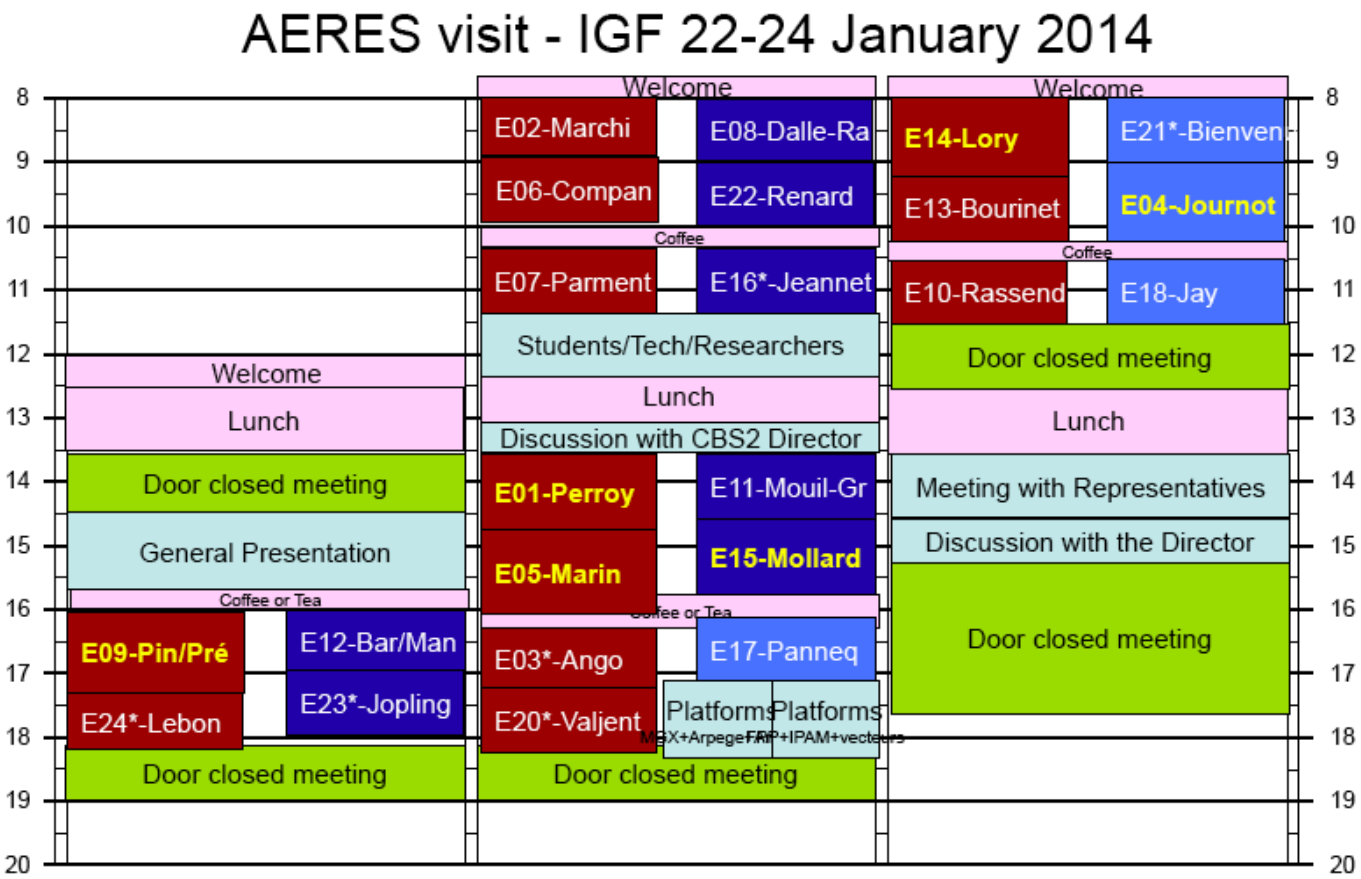
Address : 141, rue de la Cardonille

34094, Montpellier cedex 05

Specific premises visited: Platforms

Programme of visit:

The visit took place from January 22cd to January 24th 2014 in the IGF buildings. A general presentation of achievements and plans of the Institute was made by the director. Thereafter, the experts committee was split in two groups, and each team was presented by its (proposed) leader(s), followed by questions, in the presence of team members. Subgroups of the experts committee met students and post-docs, technicians and engineers, and staff scientists in the absence of the management and other categories of personnel, and the technical platforms hosted by the IGF were visited. Representatives of CNRS, INSERM and Montpellier Universities 1 and 2 were also heard by the experts committee, before a final discussion with the director.



6 • Supervising bodies' general comments

INSTITUT DE GÉNOMIQUE FONCTIONNELLE

CNRS UMR5203 - INSERM U661 - Université Montpellier I - Université Montpellier II

Jean-Philippe Pin, PhD
Directeur

Montpellier, le 4 avril, 2014

Monsieur le Président de l'Université Montpellier 1
Monsieur le Président de l'Université Montpellier 2
Monsieur le Président du CNRS
Monsieur le Directeur de l'INSERM

Réponse au rapport AERES concernant l'IGF

Messieurs,

Je vous prie de trouver ci-joint nos demandes de corrections factuelles, ainsi que nos commentaires concernant le rapport d'évaluation de notre unité par le comité d'experts mis en place par l'AERES.
Nous tenons à remercier très sincèrement le comité pour son travail remarquable, et pour son rapport très favorable pour notre Institut tant concernant sa nouvelle structuration que sa stratégie pour le futur.

Je vous prie, Messieurs les Présidents, Monsieur le Directeur, d'agréer l'expression de mes sentiments les meilleurs.

Dr Jean-Philippe PIN, PhD

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INSTITUT DE GÉNOMIQUE FONCTIONNELLE

CNRS UMR5203 - INSERM U661 - Université Montpellier I - Université Montpellier II

Jean-Philippe Pin, PhD
Directeur

Montpellier, April 4th, 2014

AERES
Department for the evaluation of research units

Reply and comments on the evaluation report of the Institute of Functional Genomics (IGF)

To whom it may concern,

We would like to express our thanks to the committee for the very positive evaluation and encouraging comments. We appreciate that the committee strongly supports our recent initiatives, and the new organization of the IGF that we propose to favor interaction between disciplines and to strengthen team interactions. We were pleased to read that the committee appreciated the major efforts made to develop cutting edge technical facilities that now provide excellent state-of-the-art tools to all our research teams, as well as others outside our Institute. It is also well received that the committee recommends further support in term of personnel to maintain these facilities without impacting the research activity of the groups that get strongly involved in these developments.

We fully agree with the recommendations made by the committee, and we wish our institutions will help us along these ways. Although we do not have much comment to make on the present evaluation report, we would like to comment on two points raised in the final recommendation section.

1- The experts encourage us to apply for EU grants. Major effort will be made in the future, as indicated in our report, to improve this. Already 3 applications to the ERC will be filled in the coming year. IGF teams also participate to 3 applications for Integrated Training Networks, and to Marie Curie fellowships. Team leaders are advertised about any specific presentation of the new horizon 2020. In addition, and as indicated in our report, and supported by the AERES evaluation committee, *we ask for a dedicated EU office in our campus, that will be useful not only for the IGF, but also for the IGH and CBS*, the two other units of our campus. Although this represents an investment in term of salary by our institutions, we are convinced that this will be highly profitable for the ongoing science in the Arnaud de Villeneuve campus.
2- The experts ask for a clarification on how the team leaders are selected, what are the criteria used to maintain a team when the team leader left the unit. During the preparation of the document that we submitted to the AERES, we fully revised the internal rules book, and this specific question was already made clear, as indicated on pages 228-229 of our document provided to the AERES for our evaluation. The specific involvement of the SAB in this process is also indicated on page 230.

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Reply to the individual team evaluation reports.

Here again we wish to thank the AERES committee for the impressive work done to evaluate the activity of the 24 teams proposed for the future IGF, starting January 2015. Although I understand that the committee had to evaluate the teams that will be part of the IGF for the next period, it is a pity that the activity of the team leaving the Institute was not taken into account for the evaluation of the past activity of the unit. In that respect, I want to remind here that team E19, a former Atip-AVENIR team, has been really successful, publishing top papers (Nat Str Mol Biol 2012; Genes Dev 2011; Nat Comm 2011, 2013), with a very high international visibility in the media. This team will join the new IRB in Montpellier, maintaining its relationship with our Institute. I really consider this as a great success of the IGF.

We fully agree with the comments made, but we would like to clarify a few points regarding the teams listed bellow.

Team E01 Fagni-Perroy:

Despite excellent general comments for this team, few points need to be clarified. In particular Julie Perroy, the new leader of this team, is already managing the team for one year and has been involved long ago in the choice and elaboration of the team's projects. Accordingly, the new leader handles all the projects of the team, including *in vivo* studies and is strongly supported by the IGF direction. Furthermore the previous leader will still be part of the team to give advises if required.

Innovating issues of the project stand in the development of quantitative imaging technics applied to neurological disorders. For these innovative projects Julie Perroy obtained two financial supports for young researchers in 2013 (ANR-JCJC and "Chercheur d'avenir" Languedoc Roussillon) and will apply this year to the ERC consolidator grant.

Finally, international collaborations are indeed objectivized by co-author publications (for example: Liu J, China; Worley PF, USA ; Boeckers TM, Germany ; Smolders I, Belgium ; Bouvier M, Canada).

Team E02 Marchi:

We would like to thank the AERES committee for its evaluation and for providing important suggestions on how to (further) improve the next 5 years of research activities. In particular "…*collaborations should be developed within the IGF with teams working on other brain pathologies for which a similar therapeutical strategy could be tested*". We agree with this comment and can mention that the team leader has already devoted effort to nurture collaborations within and outside the Institute. These collaborative efforts ensure the availability of translational/clinical (human blood and brain samples) and basic research tools (e.g., knockout mice) and allows for the generation of research grants (4 proposals are currently submitted to French, European and US agencies).

The internal collaborations are with Dr. Pascussi (CR1 – Equipe Pannequin), Dr. Schaeffer (CR1 - Equipe Mollard), Dr. Rassendren (DR2 - Team Leader). Collaborations have also been established both in France (Dr. Lakhal (INRA Toulouse); Prof. Bartolomei (CHU Marseille); Dr. Thouvenot (CHU Nimes)), and at the international level (Dr. Bauer (Principal Investigator; University of Kentucky, USA), Dr. Danemann (Principal Investigator; University of San Francisco / Stanford, USA), Dr. Janigro

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(Principal Investigator; Cleveland Clinic, USA), Dr. DeCurtis and Dr. Librizzi (Principal Investigators, Institute Neurological Besta (Italy)

Team E03 – Ango

Although the developmental studies carried out by this team are on the edge of the general thematic of the Institute, the leader has well established connections with many groups working in this area in France and abroad, such that it is not isolated in the field. Most importantly, the group also interacts with other teams within the IGF, and novel collaborations were initiated recently in order to benefit from their technical and scientific expertise in molecular and cellular signaling. Thus this team is fully integrated in the scientific life of the institute. For instance, as discussed with the committee, the team proposes a very promising study on cell surface dynamic of axon guidance receptors and IGF is the perfect place to develop this project. We are convinced that the scientific and technological environment offered to this team at the IGF, is a real chance to tackle novel questions with innovative approaches that would not necessarily be possible in a pure "developmentally" oriented laboratory.

Team E04 - Journot:

The committee encourages the team leader to find ways to decrease his workload resulting from the management of the MGX facility and the service unit BioCampus, in order to save time for his excellent research program. We would like to mention here that one professor and two assistant professors in statistics are proposed to join the team in January 1st 2015. These statisticians have an excellence experience in analyzing sequencing data including RNAseq and NGS. They already collaborate with the bio-informatics group of the MGX facility. Much is expected from their full-time research activity in the team to analyze genes differentially expressed.
Most importantly, their arrival in the team will lead to an important r-organization of the group, with the specific aim to give the team leader more time for his research activity. Indeed, it is already agreed that one of the assistant professor, Chrystelle Reynes, will take over the MGX facility responsibility within the next year. Her training as both a bio-statistician and an agronomy engineer give her all the experience and knowledge to assume such a responsibility.

Team E06 - Compan:

The team leader want to highlight that if she has published only two papers as first/last authors this is because of the time spent to develop international and national collaborations, as well as time spent on industrial collaborations that do not lead to publications. In total the team has published 7 original papers in the period (not 5): as co-authors: PLoS One 2008, Endocrinology 2009, J Biotechnol 2009, Obesity 2011, Pulm Pharmacol Ther 2013; and as last author: PLoS One 2010, Trans Psy 2012. In addition, a short review in which data from the team have been included has been published in WIREs Membrane Transport and Signaling in 2012.

Regarding the valorization aspect of the work, a patent application has been filled that led to a family of 3 patents (EU 2011, Japan 2011, USA 2013) and two others are still being negociated in the USA.

The team leader agrees that a “little caution is required in extrapolating from” animal model behavior and related signaling pathway “to the complexities of human eating disorders”. However it is

encouraging to note that following their studies, few reports from other groups show that the concentration of the serotonin 4 receptors (5-HTR4) is modified in the brain (nucleus accumbens) of overweight humans with hyperphagia.

In the report, it is stated “It will be challenging to make progress in all the proposed work with a small team and it was not clear how different aspects of the work would be prioritized.” The first part of the primary project has been pre-selected by ANR in collaboration with two other national teams (S. Wiener, collège de France, P. Gaspar, INSERM). The second part has been selected by FRM for a full evaluation. These two parts of the project will be finalized if they are accepted, and alternatively, we will adapt with potential industrial partners to pursue and further orient our efforts. For the long-term project, the leader agrees that given the size of the team, they cannot handle totally the long-term project. Consequently, they have planed to set out collaboration with several MD-researchers (MD-PhD, Pr. J. Bringer, Dr. G. Gastaldi, Pr. C. Sultan, Dr. L. Mmoun, Dr. S. Guillaume mainly from the medical school and CHU of Montpellier). Today, a hospital grant has been obtained. Both the short and long-term projects represent two specific objectives clearly interconnected through a translational approach, but are systematically related to only one focus aims at studying how anorexia is interconnected to addictive behaviors.

In conclusion, the main ANR-Grant ANR-SERFEED obtained by this team has been finalized on 2013, april 30th, and in addition to the already published work, 3 additional papers are being prepared, two of them being almost ready to be submitted. We can reasonably hope that these research articles will be therefore published as first/last authors. Please note that the final report of the ANR-SERFEED has been selected by the ANR-committee has a “projet phare”.

Team E07 - Parmentier:

We wish to thank the committee for their very supportive words regarding the past and future activity of this team. Note that the departure of a senior researcher is actually considered by the team leader as an opportunity to focus more the research programs conducted by the team.

The group plan to increase its international visibility, first by publishing their recent data in high profile journals, and by preparing review articles. The group is well aware of the urgent need for fund raising and already submitted several grant applications including those submitted to LECMA and France Alzheimer.

The committee recommendations suggests that the group might be too isolated, and would benefit from the arrival of another group working with Drosophila as an animal model. We would like to mention that the team is part of the large "fly" community of Montpellier (several groups at the IGH, one at the CRBM, another at the INM) that organizes regular "fly meetings". This allows the group to exchange ideas, techniques and fly lines, and also to have access to the fly facility located in the neighboring institute IGH. Of note, the group has constant interactions with other drosophila groups working in neuroscience, such as that of JM Dura with whom they have a recent common publication (Redt-Clouet et al. Eur J Neurosci 2012). The team also established collaborations with teams from the IGF including that N. Marchi (with F de Bock) for electrophysiological recordings (publication just accepted Lepicard et al., J Neurosci, in press), and from the IGH with the K. Rogowski's group on microtubule polyglutamylation. They also have on on-going collaboration at the "Institut des Neurosciences" de Montpellier with P. Bomont (mammalian, and human group) on giant axonal

neuropathy, and that of A. Andrieux (mammalian and human team at the Grenoble Institute of Neurosciences) on the study of STOP-like proteins. The latter examples illustrate the clear ambition of the team to validate in mammals their findings in Drosophila.

Team E08 – Dalle & Ravier:

Regarding the comments raised in the "weakness and threats" part, we have the feeling that the jury thought that Stéphane Dalle will leave the laboratory to concentrate on the spin-off company. We would like to emphasize that it is not the case.

The research project for the next five years is based on the previous activities of this team, and is divided in two specific aims that are fully complementary and interconnected. The responsibilities of each co-leader were defined in the main written document, even if we realize after reading the evaluation that it was not clearly stated during the oral presentation in front of the jury.

The first specific aim is to determine more precisely, by dynamic studies, the signaling pathways engaged by glucose, G-protein coupled receptors (GPCRs) and tyrosine kinase receptors (TKRs), and to determine the hierarchy of the activation of second messengers in b-cells. Magalie Ravier was already identified as the leader of this specific aim. A study, that she will sign last author, will be submitted regarding the role of the kinase ERK1 in b-cells *(Diabetologia abstract 2013; manuscript in preparation)*. Additionally, a PhD student (Nina Roberts) has been recruited under her supervision to fully develop the ongoing project of the dynamic recruitment of scaffold proteins (β-arrs) and signals ($[Ca^{2+}]$, cAMP, ERK1/2) under glucose, GPCRs and/or TKRs activation.

Stéphane Dalle is more involved in applied and translational researches. In that sense, he is the leader of the second specific aim that will determine whether prediabetic (chronic exposure to free fatty acid) or diabetic (chronic hyperglycaemia and hyperglucagonemia) environments affect β-cell responses to extracellular stimuli, and the clinical efficacy of antidiabetic drugs such as GLP-1 analogues (concept of GLP-1 resistance). A study that he signed as last author, is under submission, reporting the inflammation impact on the b-cell responsiveness to GLP-1. In addition, a PhD student (M. Roussel) has been recruited under his supervision, to study the adverse effects of chronic hyperglycemia and glucocorticoids on the clinical efficacy of antidiabetic drugs.

The jury is concerned by the scenario where the start-up (created in April 2014 and named Diabgen) would face problems. It is noteworthy that since the presentation, the situation has evolved. A contract giving the exclusive license to develop the patent has been given to the start-up Diabgen, and signed between the INSERM-Transfert/SATT AxLR and Diabgen. Moreover, the start-up Diabgen is already engaged in official discussions with industrials partners to fund and to develop specific scientific/medical programs aiming at the patent valorization. In line with L-413 article from INSERM, Stéphane Dalle will devote 20% of his time to act as a main scientific consultant in this start-up.

Team E14 - Lory:

We want to highlight that one member of the team is the scientific manager of the Vectorology Core facility, an emerging BioCampus platform that is being used for many research programs in the Montpellier area.

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Team E16 - Jeanneteau:

Although the presentation discriminated the two ongoing projects in the lab, the team is fully dedicated to achieve all the scientific objectives. To confirm the unity of our nascent team, a common project [submitted for review] aims at disrupting in vivo the function of the V1b-CRHR1 heterodimers in the pituitary-adrenal axis of stress using the full spectrum of expertise's from both the Guillon's and Jeanneteau's groups.

Team E17 - Pannequin:

We first want to acknowledge the AERES committee for this really extensive report, and would like to provide answers to 3 specific points raised:

1) "The team should develop a research axis dedicated to the better understanding of the molecular mechanisms involved in progastrin actions, allowing publication of team's findings in high profile journals."

Progastrin (PG) has been shown to be biologically active since almost 20 years, thus mechanisms and signaling have been largely described by our team and others (Ferrand A, Cancer Letter 2006), including modulation of both Wnt and Notch pathways by PG through deciphered mechanisms (Pannequin J, Gastroenterology 2007 and Cancer research 2009). Moreover, recent unpublished results demonstrate that PG is important for cancer stem cell survival, which led us to perform both transcriptomic and metabolic analysis. Nevertheless, the PG receptor remains unknown but our team has recruited a full time engineer for 3 years to identify it, within collaboration with a pharmaceutical company. Although several candidates have been identified, we could not present this project in details for confidentiality reasons.

2) "Considering deeper interactions and collaborations with other teams involved in similar topics within the IGF and outside might also be valuable."

Within the institute we have several collaborations and some of them are funded or letter of intention have been selected on specific projects (Cancéropole GSO, INCA, ANSES). Collaborations with Philippe Jay's team have been fruitful these last years as 4 papers, a review and a patent have been published together. Since our thematics are not similar but complementary we have moreover future projects in perspective.

Furthermore, we have developed collaborations and discussions leading to a real network with other teams working on cancer, (Melhen, Ginestier, Cheweiss, Roche, Robine…). As an example, we obtained an ANR grant in 2008 with Serge Roche (CRBM, Montpellier) and now our teams are both involved in the alliance contract with Servier laboratories. This collaboration has led to common publications (Naudin C, Nature com 2014 and Sirvent A, Oncogene 2010).

Finally, the present team leader has initiated the creation of a cancer stem cell consortium with different teams in South of France (Marseille: C. Ginestier, Nice: T. Virolle), the goal being to join the already existing European consortium.

3) "The international visibility of the present team leader could also be improved"

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Patents and links with industry have been a real obstacle for visibility. This will be corrected within the next couple of years. Indeed, recent work within the team (directed by Julie Pannequin since September 2012) has allowed for the accumulation of data that are either submitted (Planque C, Targeting the nuclear receptor PXR sensitizes colon cancer stem cells to chemotherapy) or in preparation (Grillet F, A circulating tumor cell line with cancer stem cell attributes in human colon cancer and Giraud J, Progastrin is essential to maintain the cancer stem cell state in colorectal cancer). Julie Pannequin will be last author in these 3 publications. The data will also be presented in national and international meetings in order to increase visibility of the team's work.

Team E18 - Jay:

We acknowledge the very positive feed-back on Team E18 « Self-renewal and differentiation of epithelia », highlighting the quality of the past activity and publications, the excellent reputation of the team and the originality of the future projects based on highly relevant genetic animal models.

The evaluation committee also mentioned the moderate size of the group and suggested to increase the level of interactions with the other IGF group interested in colon cancer.

The size of the team is not fixed but changes permanently. For instance, a year before the evaluation, there were two additional postdocs, one additional PhD student and one additional technician. At present, the group is in a smaller configuration but is recruiting one engineer, an additional permanent researcher (Nathalie Coutry) will join the group at the end of the year, and additional people will be hired as soon as new research grants are obtained (several applications are pending).

Although the scientific projects of the Jay and Pannequin teams are tackling distinct and complementary questions, the two groups have a long history of collaboration that led to multiple joined publications (Darido et al. Cancer Research 2008; Joubert et al. Médecine Science 2009; Diouf et al. JBC 2009; Dupasquier et al. J. Cell Sci. 2009; Escobar et al. Nature Comm. 2011). Such obvious collaborations were probably not highlighted enough in the Jay and Pannequin presentations to the committee, resulting in some misunderstanding.

Team E21 - Bienvenu:

The team acknowledges the committee for recognizing past grant application successes and the strong involvement of the team toward technology transfer by the preparation of several patents. The group leader agrees with the observation of the jury about the urgent necessity for the team to focus its research plan.

1- With the mentoring of the director of the institute (JP Pin) and the director of the department (P Jay), the team leader decided to gear the scientific strategy of the team toward the preparation of a single publication. This publication focuses deeper on one aspect of the avenues opened by the preliminary data of the team and will be ready to be submitted within few months to strengthen the international visibility of the team. This first work published with the IGF as the host institution is meant to illustrate the transcriptional impact of Cyclin D1 against cell death in cancer cells and in a CDK4 kinase independent manner.

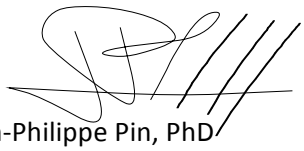
2- Afterwards deeper studies on the mechanism of recruitment of Cyclin D1 on the DNA will be fully developed within the team.

3- Only at this time, collaborations that have been on hold for the first study, will be reactivated to challenge the protective role of Cyclin D1 against cell death in several physiological models *in vivo*. While these inter-disciplinary collaborations with other groups from different departments of the IGF are strategically encouraged by the direction of the institute, they also represent the opportunity for the team to increase the number of rapid publications with corresponding authorship. These collaborations will be pushed by common grant applications with the head of the team as a project leader, in order to strengthen the scientific "niche" of the team on longer terms.

4- Then in parallel, on the occasion to communicate abroad about these results at international conferences and to increase the workforce capacity of the team with permanent researchers, post-doc candidates abroad will be encouraged to postulate to national research institution hiring contests with the team as a selected spot for their future career.

I wish you would find this information useful for the final evaluation of our unit.

Sincerely yours,



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nouvelle université de Montpellier
un projet, une ambition

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Montpellier, le 17 avril 2014

Référence : JP. PIN : S2PUR150008518-IGF-Institut de Génomique Fonctionnelle

Messieurs,

Je tiens à remercier le comité de visite AERES pour la qualité de son rapport d'évaluation concernant l'Institut de Génomique Fonctionnelle dirigé par M. Jean Philippe PIN

J'ai bien noté les remarques émises par le comité de visite et je veillerai à ce que celles-ci soient prises en compte par le directeur de cette structure de recherche.

Vous trouverez ci-joint les corrections factuelles et les observations formulées par le directeur et les équipes de de cet institut.

En tant que tutelle Universitaire de cette structure de recherche, je n'ai pas de remarques supplémentaires.

Je vous prie d'agréer, Messieurs, l'expression de mes salutations les plus respectueuses.

Philippe AUGE
Président
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