agence d'évaluation de la recherche
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Section des Unités de recherche

AERES report on the research unit

Institut de Pharmacologie Moléculaire et Cellulaire

From the

University of Nice

CNRS

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Le Président de l'AERES

Didier Houssin

Section des unités de recherche

Le Directeur

Pierre Glorieux

January 2011

Research Unit

Name of the research unit: IPMC

Requested label

N° in the case of renewal: UMR6097

Name of the director: Pascal BARBRY

Members of the review committee

Committee chairman:

Mr Daniel CHOQUET, University of Bordeaux, FRANCE

Other committee members

Mr Enrique RODRIGUEZ-BOULAN, Cornell University, New York, USA
Mr Ofer MANDELBOIM, Hebrew University, Jerusalem, Israël
Mr Nicolas LE NOVERE, EMBL-EBI, Hinxston, UK
Mr Jia-Yi LI, Lund University, Lund, Sweden
Mr Huib MANSVELDER, VU University, Amsterdam, The Netherlands
Mr Leszek KACZMAREK, Nencki Institute, Warsaw, Poland
Mr Rodrigo A. CUNHA, University of Coimbra, Coimbra, Portugal
Mrs Daniela PIETROBON, University of Padova, Padua, Italy
Mr Jamel CHELLY, Cochin Institute, Paris, France
Mr Ralf JOCKERS, Cochin Institute, Paris France (CoNRS member)
Mrs Catherine PICART, University of Grenoble, France (CNU member)

Observers

AERES scientific advisor

Mrs Catherine DARGEMONT

University, School and Research Organization representatives

Mr Stanislas TOMAVO, CNRS
Mr JM LARDEAUX, Nice University
Mrs Catherine LABBÉ-JULLIE, INSERM

Report

1. Introduction

- Date and execution of the visit

The site visit took place in Sophia Antipolis on January 25 to 27th, 2011 and was conducted by an international team of scientists with expertise in the area of scientific interest represented by the 19 teams of research being evaluated. After presentation of the unit overall past activity and future strategy, each team presented its own past accomplishments and project for the next 4 years in the presence of all team members.

- History and geographical localization of the research unit, and brief presentation of its field and scientific activities

Founded in 1989 by Professor Michel Lazdunski, the Institut de Pharmacologie Moléculaire et Cellulaire (IPMC) is a joint unit between the Centre National de la Recherche Scientifique (CNRS) and the University of Nice Sophia Antipolis (UNS). It has been directed by Doctor Pascal Barbry since 2004. Dr. Barbry is seeking a third mandate as a director.

The IPMC is located in the campus of Sophia Antipolis. A new wing largely dedicated to neuroscience has recently (2008) been added to the center, amounting to a total of 8000 m2 for around 200 people (among which 66 researchers and 39 technician/engineer/administrative with tenured positions). The number of teams has grown from 10 to 19 in the last 5 years.

The main scientific areas of IPMC have evolved in the last decade from a past strong focus on ion channels, their pathophysiology and pharmacology to a broader interest in neuroscience (mainly neurodegenerative diseases but also mental retardation), cellular and integrative biology (ion channels, membrane properties and transport, mechanosensitivity, phospholipases), immunology (mainly inflamation and NK cells), genomics and post-genomics (neuropeptide secretion, high throughput methodologies and functional genomics of epithelia and adrenal glands).

- Management team

The Research Unit will be directed by Pascal Barbry and an executive committee composed of the director and at least 2 group leaders. A team council consisting of the individual team leaders acts as a complementary body to the lab council.

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	7	9
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	47	57
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	44	39
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	40,6	39
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	12	
N6: Number of Ph.D. students (Form 2.7 of the application file)	13	
N7: Number of staff members with a HDR or a similar grade	29	35

2 • Overall appreciation on the research unit

• Summary

The IPMC is an international class multidisciplinary research center that has strongly evolved in the last years. Initially largely focused on ion channels pharmacology and pathophysiology under the directorship of Michel Lazdunski, it has broadened its scope to encompass many aspects of functional genomics, with a net diversification, in particular towards neuroscience. The major re-organizational work, which has been carried out during the last years, has originated in large part through the recruitment of four external new groups (including 3 ATIP laureates), the splitting of the former Lazdunski team in 3 new teams and the recent addition of an INSERM team. IPMC thus hosts scientists at all levels of seniority and very good projects. Senior groups, some of them with an excellent worldwide reputation, are complemented by many junior groups. The new recruitments are very good to excellent with regard to originality, quality, and potential. The institute hosts a number of technological core facility, mostly in the area of functional genomics, several of them being of national level. The institute has overall a very good scientific output and recognition, and a strong implication in technological developments and technology transfer.

• Strengths and opportunities

- Overall, the IPMC presents a good scientific production with several high impact papers and a good level of funding. Several teams are clearly of top international level
- The committee appreciated the good attractiveness for recruitment of dynamic young investigators as new team leaders that bring particular strength in new methodologies and research directions, particularly neuroscience.
- The good organization of core facilities is recognized at the national level
- The Institute presents a very good technical expertise in ion channels; pharmacology, functional genomics, with a good activity of technology transfer
- The committee appreciated the pleasant working atmosphere
- Development of epithelial research in several teams opens the way for it being a global strength of the institute
- More generally, the diversity of the expertise of the teams open the way for ambitious transversal projects

• Weaknesses and threats

- Lack of scientific focus: though the overall research activity of the institute is oriented mostly towards neurosciences, developed projects and biological issues are extremely diverse and include cancer, pulmonary disorders, inflammation, epithelium cells…
- As a consequence, there is a feeling of a lack of strategic vision for the institute's general ambition and scientific objectives that would render the IPMC more visible at the international level
- Efficient interaction and complementarities between teams does not appear as a priority for the institute and the executive committee.
- The same comment applies for the interaction between the institute and clinical and hospital leaders and professionals. Though some clear specific interactions and collaborations could be pointed out, the potential of the institute for translational medicine and research may be more important and an active discussion for efficient organization could be considered.

- For some groups : one might wonder if the environment of the institute is adapted
- The committee observed a certain heterogeneity in the scientific productivity level of the different teams
- The IPMC suffers from a lack of attractiveness for PhD students and post-docs, particularly of foreign origin
- The committee could note a lack of transparency of the general governance and low general Involvement of the group leaders in the institute's decision making process
- The property status of the building is still unclear

- Recommendations to the head of the research unit

In general, the diversification of the institute's scientific projects and emphasis on the development of cutting edge technologies for functional genomics is laudable. However, it is also the most important threat for the institute to be unfocussed and too much technology driven. A clear thought should be considered to rethink the vision, establish a 10 years strategy. One process to this aim could be to enhance and strengthen some scientific interactions between groups. Other recommendations of the committee are:

- Rethink the decision making process and improve the transparency of the governance
- Actively involve all group leaders in the decision making process, in particular regarding allocation of resources (mainly space and technical personnel)
- Develop mentoring of students and young group leaders
- Put more emphasis on attracting foreigners
- Encourage a more ambitious publication policy and application to international grants
- Build an image for the center visible from abroad
- Recommend stronger support by the university for improving the conditions for the student (transport, food)
- More space should be allocated to successful teams

- Production results

A1: Number of permanent researchers with or without teaching duties (recorded in N1 and N2) who are active in research	66
A2: Number of other researchers (recorded in N3, N4 and N5) who are active in research	62
A3: Ratio of members who are active in research among permanent researchers [(A1)/(N1 + N2)]	1
A4: Number of HDR granted during the past 4 years	7
A5: Number of PhD granted during the past 4 years	26

3 • Specific comments on the research unit

- Appreciation on the results

The overall productivity has been very good, reaching an excellent level for some teams. The institute contributed to significant advances in our understanding in several key areas of biology including for example i) the role of ion channels in a variety of important functions such as pressure sensing, calcium homeostasis, depression or pain, ii) the cross-talk between molecules involves in Alzheimer's and Parkinson's disease, iii) immunological mechanisms responsible for asthma and potential therapeutic strategies, iv) the mechanism for membrane curvature sensing, etc...The institute has developed several original projects along these lines that are internationally recognized.

A majority of teams of the institute are competitive at the international level in their field, as can be assessed by a large number (51) of >10 IF papers. About a quarter of the teams are world leaders in their field. Overall, the IPMC authored over 400 publications with an average IF of 7.1.

26 Ph.Ds. have been defended during the past four years, which is a comparatively low number that should be improved.

The institute has placed a strong emphasis on technological developments, developing a large number of state of the art core facilities in functional genomics (Ibisa), cellular imaging (ibisa), proteomics, animal care, bioinformatics etc... Application of the research either through the clinics, or through technology transfer, has been particularly good, with 22 patent applications filed and 6 patents internationally extended. IPMC has also been associated with the creation of several biotechnology companies (ImmunoSearch, VenomeTech and Theralpha). Strong collaborations between the Hospital and the Functional Genomics Platform or between various groups and clinicians have also been established and fruitful.

- Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners

A few scientists at the IPMC have received high honors, such as the Silver Medal of CNRS, an ERC grant, the prestigious gold medal of the Jung foundation, the Jansen prize, the Bettencourt-Schueller Prize, with a total of around 30 awards for the institute.

Researchers at the IPMC have been invited to over 180 international conferences, which is a rather modest number considering the 66 permanent researchers of the institute and which may reflect the fact that not all teams have reached international visibility.

The IPMC has managed to recruit four excellent new young group leaders including 3 from abroad. Three of them have been selected for the prestigious ATIP young investigator grant. In addition, the IPMC has recruited 6 new researchers on permanent positions. In comparison to this excellent attractiveness for new group leaders, the institute has performed comparatively poorly in terms of attractiveness for students and post-docs. With only 23 PhDs and a little over 40 post-docs (little from abroad) attracted in the last 4 years, most of the team's age pyramid lacks young blood. This is a recognized weakness, partly explained for the PhD students by the remote location of the IPMC from the main university campus. This drawback should be compensated by i) trying to improve student's condition (transport and food) in Sophia-antipolis and ii) a more aggressive policy of recruitment of students and post-docs abroad for example by putting together international training programs or participating to European networks.

The IPMC has been successful in raising funds from various sources: ANR, European contracts, industrial contracts, foundations, charities, and local authorities CG 06, PACA Region... with 1.5-3M€ per year in external contracts. The amount of funding from external sources (24.8%) as compared to recurrent money from CNRS/INSERM/university is good but could be improved. In particular, participation to international networks such as EU grants is relatively modest, with the notable exception of the recent ERC grant to team 1. The IPMC has clearly the recognition and competences to be an attractive partner in EU consortia. An active policy to encourage and mentor participation/coordination by the various teams to EU grants should be implemented.

One question is how the INSERM will participate to funding of the institute when the former INSERM team will merge with this CNRS unit

Obtention by the teams of industrial contracts is generally good, in line with the good technology transfer and patent application of the institute (22 patents during the period).

Both senior and newly established investigators have collaborations with European and US labs, although for many teams most collaborations are still with French labs. There also, a general policy of a greater opening to foreign labs would reinforce the visibility of the institute on the international scene.

- Appreciation on the strategy, management and life of the research unit

The research unit is broadly interested in biological entities such as ion channels, signaling molecules, hormones, neurotransmitters, receptors, proteases and microRNAs that are implicated in a variety of diseases. It aims to develop activity in Neuroscience, cellular and integrative biology, genomics and post-genomics, in the general context of diseases. For this aim, it makes use of a wide variety of multidisciplinary approaches such as physiology, rodent behavior, cellular imaging, electrophysiology, functional genomics and proteomics.

This important diversification accelerated recently with the recruitment of several teams in neuroscience together with the addition of an immunology team. As a consequence, there is a feeling of a lack of focus and lack of a clear general scientific strategy for the institute as a whole. Indeed, although neuroscience is presented a major axis for development of this institute, backed up by the recruitment of new teams, a large number of the flagship projects are in totally different areas. An effort to increase the international visibility of the institute likely goes through identification of a few well identified global scientific objectives. The emergence of inflammation and epithelial biology as a major strength of the institute, which can be related with work on neurodegenerative diseases, could be one opportunity.

The variety of competences present in the institute, as well as their wide organization in core facilities is impressive and greatly participates to the attractiveness of the institute and unanimous satisfaction of the different teams about the availability of different techniques. Facilities include Functional Genomics, proteomics, Cellular imaging, animal care, bioinformatics...

The important dedication of human and financial resources to these core facilities is an excellent strategy that should in the long run foster the development of the institute and the recruitment of other team leaders, students and post-docs.

As a drawback, there is a general lack of technical support dedicated to individual teams, with many senior teams missing permanent staff technical personnel and having to rely on temporary recruitments. While it is laudable that the institute dedicates important resources to core-facilities, a more balanced distribution of technical personnel between facilities and teams should be envisioned.

The research unit staff members contribute to teaching, although there is a worry for a decrease in the number of personnel with teaching duty, and to the structuration of the research at the local level: many staff scientists are involved in teaching activities.

Members of IPMC have organized 19 national or international scientific meetings. To facilitate communication between staff within the Institute, a scientific retreat is organized. Seminars by external speakers are regularly organized (279 have been held during this period), and several programs of internal seminars are ongoing.

The meeting with ITA involved both the personnel attached to teams and core facilities. They drove the first part of the meeting, through a well prepared presentation. They expressed their good participation to the life of the institute, the organization of the lab council, the lifelong training. They were generally happy about their participation as authors to publications, although disparities existed. There was a marked feeling for a difference in career development between ITAs working in teams and those working for core-facilities, the latter being favored. The absence of clear knowledge of the mechanism regarding the decisions relating to their careers was striking.

More generally, regarding the governance of the unit, the general impression was that there is a lack of transparency and that the mechanisms for allocation of resources is opaque. The committee could not understand the mechanisms for allocation of space or of technical personnel to teams. Similarly, the rules for career promotions, bonus allocation or mobility of ITAs are unclear. This lack of transparent governance was repeatedly expressed during face to face meetings with team leaders, with ITAs and researchers.

Regarding PhD students, they did not seem well informed about the various career development paths. There seemed to have a lack of information on European opportunities and not enough encouraged to participate to meetings. A PhD mentoring system seemed to be lacking at the institute level.

The evaluation committee strongly felt that efforts should be made to improve the general governance by i) improving the communication between the governing bodies and the personnel and explaining better the rules and rationale for resource allocation, ii) implicating more the different group leaders in the decision process at the institute level, maybe by increasing the size of the executive committee, or by giving a more important decisional role to the team leader committee, iii) improving the career development follow-up for all categories of personnel, including ITAs, students, post-docs and researchers, maybe by creating a dedicated career development committee.

- Appreciation on the project

On the whole, the institute hosts a series of good to excellent projects. However, as described above, the IPMC represented mainly a collection of individual projects, rather than an organized effort toward solving well identified major questions. The committee felt a need to decide on stronger international visibility as a whole.

Team 5 was felt in danger for the future due to absence of a mainstream project, low funding and lack of sufficient personnel in the project.

Team 10 failed to convince on the solidity of its strategy, both due to the absence on an ambitious project and the disconnection of the new projects from the main stream of the team.

Allocation of ressources, in addition to beeing somewhat unclear, was not enough concentrated on big projects.

The institute hosts several individual cutting edge projects, but several team projects could be more ambitious. There is a lack of institution level ambitious project

4 • Appreciation team by team and/or project by project

- E1 Dynamics of lipid membranes and protein coats
- **Team Leader Bruno ANTONNY**
- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	4	4
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	4
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results

During its past activity, the E01 team (Dynamics of lipid membranes and protein coats) has discovered the ALPS motif and has evidenced the role of Golgin GMAP-210 as a curvature sensitive membrane tether. These findings are highly innovative. The publications of the team are of very high quality with 21 articles in the past years (including Cell, Nature Struc Mol Biol, Nature, Science, EMBO J, PNAS) as well as five invited conferences in international meetings (Gordon conference, EMBO meeting). The team has also an internal collaboration with team E07 and external fruifult collaborations (with Curie Institute, Institut Monod…) that are acknowledged by common publications.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

Two members of the team received prestigious CNRS medals (one as bronze and one as silver) and the group leader is an EMBO member. The team has also been able to attract young researchers (CNRS researchers). The fundings of the team over the last period have been based on academic research programms, such as ANR Programme Blanc.

- Appreciation on the strategy, management and life of the team

The recent selection of the team for a prestigious ERC advanced grant is a further acknowledgement of its excellence and secures funding for the next years.

- Appreciation on the project

One of the major focus for the future is to further understand how amphiphatic helices function as membrane sensor. Another focus is to study how ALPS motifs and ARF proteins cooperate to organize membrane remodeling events, including vesicle formation, membrane tethering, and lipid transfer. The planned work on different varieties of the ALPS motif that are candidate to perform various types of tethering functions between organelles/vesicles, is ground breaking. Overall, the project is very well organized, original and focused. It combined different approaches from biochemistry to biophysics (use of artificial membranes and computational biology. The repartition of the researchers between the different sub-projects is well-balanced.

- Conclusion :

  - Summary

In summary, the committee was very impressed with the group leader's presentation, progress and productivity during the past 4 years and with his plan for the next four years. A clear conceptual thread links all the work by the group, which blends beautifully biophysics, biochemistry, computational biology and, more recently, cell biology. The discovery of novel curvature sensors during the past four years open the way to understanding major questions in interorganelle communication and cholesterol transport.

  - Strengths and opportunities

-Pionnering studies on curvature sensors and development of dedicated assays (creation of a "niche").
-Excellent technological expertise in biochemistry, biophysics, cell biology and computational biology
-Numerous fruitful collaborations

  - Weaknesses and threats

-a bit scientifically isolated in the Institute

  - Recommendations

The group is encouraged to develop internal collaborations with the E09 team on mechanosensing. The committee would also advice the laboratory to give more space to this group, which will significantly increase in size thanks to the ERC advanced grant very recently attributed to the group leader.

- **E2 Physiological Genomics of Eukaryotes**
- **Team Leader Pascal BARBRY**
- **Staff members (on the basis of the application file submitted to the AERES)**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	4	6
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	6	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	0
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	
N7: Number of staff members with a HDR or a similar grade	2	3

- Appreciation on the results

Over the last four years, research activities and projects of this team have focused on functional genomics applied to the study of functions and pathologies of epithelia. Examples are the identification of the complex interplay between HIV infection and microRNA machinery, the characteristic molecular signatures associated with lung and hepatic pathologies, characterization of the impact of microRNA during multiciliogenesis, hypoxia, etc. The investment on microRNA has been very successful. To concentrate on this topic for the next 4 years is very sensible. The impact of the research is limited, with some flagships due to successful collaborations.

The group publishes steadily, 38 publications and reviews, which is on average 1 publication per year and per research staff. The publications are in solid journals, including a *Science* and a *Cell* although not in first or senior position. 13 papers have been published in first or last position. The group has two patents and many collaborations with clinic and industry.

- Appreciation on the strategy, management and life of the team

Although scientifically excellent, the group's collaborations, funding sources and meeting organisations are largely national.

Senior scientists are often invited to present their results, mostly in European conferences. 15 invitations to national and international meetings (European respiratory congress, European cystic fibrosis…).

The attractiveness, the ability to recruit high level scientists, post doc does not appear in line with the up-to-date developed methodologies and topics. Post-docs and students are all from France. The number of tenure researchers in the group is growing. However, the recruitment is mostly not external (1 promotion, 1 movement within IPMC and 1 CR2 recruitment).

The ability to raise funds, and participation in European projects is very good with 2300 KEur have been raised from 11 different sources, although only one international funding (European FP7) is listed.

Senior scientists and 2 post-docs are teaching locally. Their collaborations with different local actors, public or private, contribute to the insertion of IPMC in the local environement.

Of note, the PI also runs the functional genomics core-facility labeled by the national structure IBISA. The research team develops new technological and bioinformatics tools for the platform, mainly in high throughput sequencing. The core facility, not evaluated here, is a valuable ressource for several teams of the institute. Its activity are well separated and complementary to those of the research team.

- Appreciation on the project

The objectives of the project deal with the understanding (i) of the impact of miRNA in normal and pathological epithelial tissues (differentiation, regeneration and transformation of epithelium cells…), and (ii) molecular mechanisms enabling different species of miRNA to regulate their targets. All resources will be concentrated in the study of small non-coding RNAs, which is a very sensible decision. The topic of miARN is of large interest and the focus of many research groups, and the experience and knowledge of the team in this field represents an advantage and significant results and contributions could be expected. However, the presentation of the project lacks convincing thoughts about the overall vision, and hypothesis concerning the role of miRNA in biological processes. The proposed methodological approaches are sometimes not clearly related to the proposed objective.

- Conclusion :

  - Summary

This research team is strongly technologically driven, with a good scientific production and as an added value a contribution to the activity of the functional genomics core facility. As a drawback, the research team somewhat lacks research focus based on an ambitious biological question.

  - Strengths and opportunities

The focus on miRNA in epithelial cells. The development of the core facilities. The project and proposed investigations are in continuation with previous work and the results already obtained. The topic of miRNA is of large interest and the focus of many research groups, and the experience and knowledge of the team in this field represents an advantage and significant results and contributions could be expected. The platform is now mature and will play an important role to assist the research.

  - Weaknesses and threats

The presentation of the project lacked convincing thoughts about the overall vision, and hypothesis concerning the role of miRNA in biological processes in vivo.

  - Recommendations

The topic of miRNA is highly competitive, promising and many basic scientific issues remain to be addressed. This team has some experience and skills in the field and should have more ambitious objectives to become internationally competitive. Keeping a focus on the physiopathology of epithelial structures will help acquiring visibility. In that respect the team should develop connections with other groups at IPMC working on epithelial cells.

- **E3 Physiopathology of Intellectual Disability**
- **Team Leader Barbara BARDONI**
- **Staff members (on the basis of the application file submitted to the AERES)**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	4	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	0
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results

This team studies the molecular basis of mental retardation in Fragile X syndrome (FXS) and non-syndromic intellectual disability associated to FRAXE. The topic of Fragile X syndrome and FMRP function and its role in the development of cognitive functions is highly competitive. The PI has been working in the field, mainly the function of FMRP, for a long time even after her move from IGBMC in Strasbourg to Nice. The PI tried to find her own niche within the competition. They provided some original contributions about the molecular mechanisms underlying the interaction between FMRP and mRNAs, and proteins interacting with FMRP, in particular regarding the implication of FMRP in pathways regulated by Rac through FMRP interaction with CYFIP. More recently, the group showed that FMRP contributes in the regulation of SOD1 through interaction with mRNA (different from G-quartet structure) . This work is very relevant to neuroscience and society, and the team takes original approaches to address the issues at hand. Judged by the publications, the work is of very high to excellent quality, with a good impact in the field.

In the past five years, this team published 18 original research papers and 3 reviews. On 14 of these, a member of the team was first and/or last author. Of special notice is the PLoS Biology paper of 2009 with the PI as senior author. In addition, 2 papers were published in Nucleic Acids Research with the PI as senior author.

The PI has several successful collaborations, one of which with a lab at the Rockefeller, NY, which yielded a paper in Nature in 2006. The collaboration with a canadian lab (Laval, Quebec) resulted in a paper in Human Molecular Genetics in 2007.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team received 8 personal fellowships, among which a Marie Curie postdoctoral fellowship.

The recruitment of two new junior scientists (CR2) is a good indication about the dynamics of the team. This should be translated into efficiency and excellent science. Attractiveness of the team is also demonstrated by the recruitment of two junior scientist and presence of two post docs. The team has a good ability to raise funds as demonstrated by the participation and coordination of National and European grants. A solid list of 12 awarded grants is provided. A funded e-Rare collaboration with a european network is listed, as well funding from foundations such as Jerome Lejeune and FRAXA and exchange grants with researchers from Italy and Australia.

- Appreciation on the strategy, management and life of the team

The team organization seems balanced. Sufficient amounts of students and postdocs pass through the team. No teaching is listed.

- Appreciation on the project

Projects for the coming years consist of FP7, FRM and e-Rare funded projects, that form part of collaborations with these consortia. Other lines of research focus on the Role of fmrp in early neurogenesis and molecular pathology of FRAXE. Most of these projects are logical follow ups of ongoing research, are very relevant from a scientific and societal view point and appear to be very feasible.

One remark is that in project 1.2 FRET experiments are listed, but no collaborator, posing the question of the existence of the required expertise in house.

Proposed hypothesis, methodologies and investigations are coherent and to some extent original (not always in line with the main stream thoughts). Though proposed investigations are pertinent and of potential interest, a better justification of their relevance with the respect to the pathogeny of intellectual disability should be taken into consideration (as the overall objective of the PI and the team is understanding of pathophysiological mechanisms underlying cognitive deficit in Fragile X syndrome). In principle all projects listed can yield cutting edge results.

- Conclusion :

  - Summary

Strong research output. Good list of research funding. Good international network. Fruitful collaborations. Relevant research plans.

  - Strengths and opportunities

Good international network. Fruitful collaborations. Relevant research plans.

  - Weaknesses and threats

Absence of permanent technical support jeopardizes continuity of research projects.

  - Recommendations

The team gained and established their place and position in the national and international competion in the field of FMRP function. Thoughts and discussions about the adequation between projects (and proposed investigations) and contribution in biological and neuronal (or other brain cells) pathophysiological process underlying the pathogeny of intellectual disability should be considered.

The team is highly encouraged to get collaborations within the IPMC off the ground, and to make more use of the in house platforms.

- **E4 Role and regulation of natural killer cells**
- **Team Leader Véronique BRAUD**
- **Staff members (on the basis of the application file submitted to the AERES)**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	0
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	
N6: Number of Ph.D. students (Form 2.7 of the application file)	0	
N7: Number of staff members with a HDR or a similar grade	1	2

- Appreciation on the results

The PI made a seminal discovery as a young researcher. She showed that HLA-E is recognized by the NK complex receptor CD94/NKG2A. This is one of the most important discoveries in the field and even today this discovery continues to influence the field quite significantly. In the past 4 years the team concentrated on two main issues; 1) Identification and characterization of new NK receptor-ligand interactions and 2) The function of NK cells in vivo and how they are influenced by T cells. In the first project the team identified the LLT1 as a ligand for CD161. They have characterized the expression pattern of LLT1 and demonstrated that it is a marker of immune cell activation. They have demonstrated that the interactions between LLT1 and CD161 inhibits NK cell activity. They have also characterized the expression of LLT1 in disease and demonstrated that it is elevated in IBD and on certain type of tumors. This was a collaborative effort with a company and therefore it is expected that several publications that have resulted from this research will be published soon.

In the second project, the team studied the NK cell interaction with DC. They showed that CD4+ T cells contributes to the activation of NK cells directly by secreting IL-2 and indirectly through IL-12 secretion from DC. Further they have demonstrated that such T cell activation is important in vivo in cases of L. major infections. To further investigate this activity they will use the NK-deficient e4pb4 KO mice. They will further investigate the IL-2 signaling pathway with regard to human cell activation in humans with polymorphisms in the IL-2 receptor.

They developed the first neutralizing monoclonal antibody against LLT1 (research collaboration with Novo Nordisk 2005-2010), patent filed in June 2010).

Quality and number of publications are not constant, but the group displays a good productivity given its size. Excellent publication in 2006 (J Exp Med with co-first author but V Braud only 4th last author), 3 further publications but only minor participation as co-author. No publications in 2007 and 2008. Two collaborative publications in 2009. Three publications in 2010, with the PI as last author (J Immonol, Immunology, J Biol Chem). Other outputs : 3 invited conferences, 1 patent application.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The PI got 3 speaker invitations and 1 chairman at international conferences in the field of Immunology and is member of scientific commitee of the meeting of the Society for Natural Immunity (2010). The team is rather small, with a low number of post-docs and students (only 1 post-doc and 1 PhD student since 2006). Funding has been obtained from ANRS and Sidaction between 2006 and 2009 and from Novo Nordisk from 2005-2010. The current funding situation is not clear. The team has several active foreign collaborators and the PI was (coauthor) in 1 publication with each partner and a local collaborator with several co-publications. mAb have been developed with Novo Nordisk.

- Appreciation on the strategy, management and life of the team

The past overall size of the team has been quite small. The recent addition of a full time researcher (CR1) who joins the team (previously at Inserm, U634, Faculté de Médecine Pasteur, Nice) is very adequate. She is author of 37 publications.

- Appreciation on the project

A major reorganization of research topics is proposed by the team leader. The new topics integrate also the research interest and expertise of the new CR member, to the team: mucosal immunity and dendritic cells (DC) in models of chemical inflammation and carcinogenesis. Three specific projects are announced : 1) Nature and function of tissue-associated NK and DCs during carcinogen-associated inflammation and tumor development, 2) Epithelial responses to topical application of chemical carcinogens that may modulate NK cell and DC functions, 3) Carcinogen-associated inflammation and tumor development in humans.

The project of the team is very relevant. One of the recent advancement in the field was the understanding that tissue resident NK cells have different function and phenotypes. The NK in the gut secrete IL-22, during pregnancy NK in the decidua secrete VEGF and during viral infection they secrete IFNg. Along this line the team proposes to study the function of tissue resident NK cells during inflammation and in tumor development.

The arrival of the new CR coincides with a new research focus of the team (role of DC and NK cells in inflammation and carcinogenesis) The projects are original and look feasable. They are at the front of the field; i.e. studying the function of tissue resident NK cells. The team already obtained most of the reagents needed to complete this project.

- Conclusion :

  - Summary

The limited size of the group and the fact that it was quite isolated lead to the limited, although adequate, productivity of the team in the past few years. The PI has now established a new line of investigation that includes new researchers and is related to other groups working on ephitilial cells in the same institute. This new line of investigation that is based on the interaction of innate immune cells with ephitelial cells in various ilnesses together with good potential of the PI will be fruitful. The team leader is now at the perfect place to continue her studies.

  - Strengths and opportunities

The strength are the originality of the work, the tools the team has already obtained, the exciting new projects through the arrival of the new CR member and the collaborations that the PI has already established within the institute. Several years of experience in the field, several active collaborations (international and local); post-doctoral fellow with good chances to be recruited at CNRS. This group will take advantage of possible collaboration on epithelial cells and immunology at the IPMC.

  - Weaknesses and threats

Past achievements are moderate. The team has been small including only two researchers and few students and postdocs. Integration of the new researchers and integration of the team in IPMC must be conducted carefully.

- Recommendations

This team should continue its new strategy. More technical help and more lab space would enable its planned growth and the requirement of new PhD students and postdocs.

- **E5 Physio-pathology of prion diseases**
- **Team Leader Joëlle CHABRY**
- **Staff members (on the basis of the application file submitted to the AERES)**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	
N6: Number of Ph.D. students (Form 2.7 of the application file)	0	
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results

The group focuses its research on a main topic, prion proteins; however, within this topic the group pursues different goals (relation with immune system, cannabinoid system, alcohol tolerance) which seem rather scattered. Each of these topics seems both novel and of potential relevance; however, the quality of the output (published papers) and its impact (ISI) are fair but far from outstanding. Nearly half of the published papers are devoted to a topic abandoned by the group. The training of 3 PhD students during a 5 years' period is also fair but far from outstanding.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The group does not seem to have a prominent external visibility, as gauged by the lack of mentioned awards and the episodic invitation to conferences and seminars. There seems to be no post-doctoral fellows in the group, which has attracted 2 Masters' students and seems to be lacking PhD students. This lack of attractability is very honestly identified by the group leader as a major threath by the group.

The track record of fund raising is disappointing and it seems rather worrying especially in recent years. There seems to be an industrial collaboration, but, oddly, this is not translated in any evident and immediate financial benefit for the group.

The group is part of a European consortium on prions, but the impact for the group of this endeavour is not evident. The list of external collaborations is also limited and their scope and benefits is also not evident for the group's performance commented in the report. Overall, there is an impression of limited insertion of the group in the international arena.

A patent emerged from the group's activity, and its exploitability seems to be under current optimization. However, as recognised by the group, the decreased general interest in prion's-related diseases may well hamper the socio-economic impact of these efforts.

- Appreciation on the strategy, management and life of the team

This is a relatively small group, with 3 personal now, and with 2 expected recruits in the next 4 years.

The future planning strangely lacks any goal of better integration of the group in the Institute's life; it seems as if the group evolves independently of the Institute, which is a main concern both for the group and for the Institute. The understanding is that teaching duties come very low in the priorities of the group, to such an extent that this aspect is not commented in the planning of activities.

- Appreciation on the project

The proposed projects all seem achievable within a 4 years' period. However, all the projects seem like fostering particular molecular details of prion's physio-pathology; hence, albeit they will probably increase current knowledge, their breath seems rather limited. There seem to be all required facilities and expertise to carry out the project. However, the manpower is limited. Certainly a main focus on prion proteins is currently original in view of the decreasing wide interest on the topic. However, none of the planned projects really stands out as a cutting edge project.

- Conclusion :

  - Summary

The research topic seems somehow out of the current mainstream, which has negative aspects (decreased visibility) but also positive aspects (niche with fewer competitors). However, the recent activity of the group seems somehow slowing-down and there is no evident planning for counteracting this apparent trend. There is a clear need for an ambitious research plan to place the topic and the group in a shinning place in the map of science.

  - Strengths and opportunities

The fact that the topic of prion's proteins is slowly slidding away from the mainstream allows people with the know how in the area and with ambitious and novel ideas to provide novel contributions without the constrains of fearful competition. The applicants seem to understand the issues at stake very well but have not taken measures to ensure that they can change the current situation.

  - Weaknesses and threats

The main weakness as the PI also acknowledged, is the low funding and lack of sufficient personnel in the project, both will affect the execution of the proposed project. There are no clear indications how the group will cope with these issues.

  - Recommendations

The first recommendation is to carefully plan for a real ambitious plan for the years to come rather than just attempting to detail molecular aspects solely focusing on the prion's proteins. One suggestion could be that the observed relation between PrP and NMDA receptor function in the models of alcohol consumption could allow 'selling' a key role for PrP as a controller of NMDA receptor function, mainly NR2B. Why not making a strong bet on a role of PrP in addiction or depression? This is both mainstream (these are major health concerns), probably more fundable and more visible (easier to publish) areas, albeit it is certainly a risky bet. Again without even knowing if the issue is pertinent, it might be an appealing subject to dig in the role of PrP in the immune system for which there seems to be strong knowhow at IPMC. Obviously, any (or other) such projects probably require merging the groups expertise with that of other groups; in fact, establishing strong collaborations with leading groups in different physio-pathological areas may be a way to bolster the groups' future activity.

- **E6 Molecular and cellular biology of normal and pathological cerebral ageing**
- **Team Leader Frédéric CHECLER**
- **Staff members (on the basis of the application file submitted to the AERES)**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	4
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	7	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1,8	1,8
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	
N7: Number of staff members with a HDR or a similar grade	3	4

- Appreciation on the results

This team is working on three major neurodegenerative diseases, namely Alzheimer (AD), Parkinson (PD) and Prion diseases. In the past 4 years, the team has made clear progresses in each research lines, and published about 40 original and review articles, some of which in the top journals, such as Nature, Nature Cell Biology, PNAS, Neuron, and Journal of Neuroscience, etc. The major achievements were on beta-amyloid production, degeneration, biotransformation and function in cell and animal models of AD and on the three PD related genes (alpha-synuclein, DJ-1 and parkin) in relation to cell death in PD models, and last, on how are processed prion protein by a-secretases and the possible link to AD pathology.

The quantity and quality of the published papers is high. The number of post-docs and PhD students seems well balanced in view of the number of research staff.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The head of group is a widely recognised major player in his field. He is part of different organizations and Editorial Boards of scientific journals and is regularly invited for conferences and requested for consultancies. Of note, one of the group members received a junior award.

The number of post-docs in the group seems to be that expected for the funds and the number of permanent staff members of the group. It would be expected that the quality of the record of publication of the group should make it easy to attract high quality collaborators from different countries.

The track record of fund raising is very good. It is based on competitive grants and contracts from the French government. Finally, albeit the head of the group has numerous links with industrial partners, this does not seem to translate into contracts with private entities. There is both in-house and external collaborations, none of which seems to be sustained or determinant for the activity of the group.

The activity of the group is on molecular mechanisms of disease; hence, the most obvious concrete consequence of the group's activity is the generation of novel knowledge, which the group has abundantly fulfilled as testified by the record of publications.

- Appreciation on the strategy, management and life of the team

This is a large team, with 14 scientists (including PhD students) and 3 technical staffs now, and with 6 more staffs in recruitment in the next 4 years.

The activities of the group do not seem to require a major integrative effort with its immediate environment. There is an in-house reported collaboration and it is hoped that the group might play a key role in the support of a newly contracted group leader. Teaching duties are only episodic.

- Appreciation on the project

They have extended the current research lines into the new research plan for the next 4 years. The plan is rather ambitious and complex. The proposal is original and innovative. Using in vitro and in vivo models of AD they will study NFkB regulation to beta and gamma-secretases, trafficking of gamma-secretase, cell death effect of AICD59 and C31 and abeta degradation and processing, with a strategy of seaking for AD progression biomarkers. In the PD model, they mainly focus on parkin transcriptional targets and the possible link between AD and PD via parkin. Last, but in a small portion, the team will continue to study regulation of a-secretase processing of prion protein and possible neuroprotective effects of processed prion protein fragment N1. The research lines are well-integrated into the whole package in the Institute. However, most of the in vivo work is based of double-crossing of different trangenic lines, which might introduce an exponential increase in cost of research. The manpower of the group is a strong additional argument to justify the feasibility of the proposed workplan.

The ressources required to fulfill the workplan seem to be at hand. There might be a concern with respect to the space allocated in the animal house, which IPMC should consider.

If one considers that the main focus of the group is centered in molecular mechanisms of neurodegenerative diseases, then most of the planned activities are really exciting. However, fitting the group's activity in the fundamental and clinical continum reveals a very focused approach on molecular aspects. Surprinsingly, a current major focus in the early phases of neurodegenerative disorders (synaptic dysfunction) is not considered in the workplan.

- Conclusion :

  - Summary

This is clearly a dynamic and successful group, with a robust past activity and an ambitious plan for future research. The team is well funded. Based on their good track record, it is most likely that they will be able to fulfill the research plan.

  - Strengths and opportunities

The group has a valuable expertise, some interesting molecular tools and several novel candidates and strategies to interefere with the demise of neurogenerative diseases. Hence, it only depends on its dynamic to allow florishing a continuous output of good quality. Finally, the exploitation of the arrival of a new group leader with a strong background on neurophysiology and with a clear interest in Alzheimer's disease might provide a great and very useful collaborative opportunity.

  - Weaknesses and threats

There seems to be a major focus on the late stages of neuronal damage. If the field finds effective prophylactic strategies, it may hamper a lot of the group's impact. Another major concern might be the excessive dependency on public money coupled with a plan of activities expected to dramatically raise the bill.

  - Recommendations

A first recommendation would be to seek more actively for private funds, as well as non-french funds to consolidate the current and planned operation. A second recommendation would be to take advantage of a newly recruited group leader to fill the current gap in synaptic and neurophysiological approaches.

- **E7 Arf proteins, cell morphology and membrane transport**
- **Team Leader Michel FRANCO-Frédéric LUTON**
- **Staff members (on the basis of the application file submitted to the AERES)**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	
N6: Number of Ph.D. students (Form 2.7 of the application file)	0	
N7: Number of staff members with a HDR or a similar grade	2	2

- Appreciation on the results

The group, which was created in 2007, studies the molecular mechanisms that coordinate plasma membrane remodeling with actin reorganization that take place during endocytosis/recycling and the development of epithelial cell polarity. Important results from the group in the past year include the finding that an exchange factor for ARF6 (EFA6) and its deubiquitination via USP9X play an important role in the development of epithelial tight junctions and the perijunctional actin cytoskeleton. These results open new avenues to understand the role of ubiquitination in the establishment of epithelial polarity and tight junctions. The research has potential to contribute significantly to aspects of cancer. The group has published in very good journals (*EMBO J 2010, Traffic, PNAS, PLOS Biol, J Biol. Chem…)*. The impact of the results is starting to result in invitations to national and international meetings (a FASEB meeting and three french conferences).

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The group has fruitful ongoing collaborations with Curie Institute, Gif/Yvette, Institut de Microbiologie de la Méditerranée, Marseille and the University of California. The collaborations have lead to publication in high impact factor journals. The collaboration with Marseille resulted in a ERC Starting grant as partner.

- Appreciation on the strategy, management and life of the team

Two group members are involved in the teaching at the University of Nice. Several Master students have rotated through the laboratory. As with other groups in the Institute, there seems to be some difficulty in recruiting PhD students to the Institute. Nonetheless, one PhD student completed a thesis and a french postdoctoral fellow joined the group funded by a CNRS fellowship.
The group has also attracted funding from multiple sources (Cancéropole, ARC, ANR). There were also several short-term FEBS and EMBO fellowships

- Appreciation on the project

The project of the team is a logical continuation of its previous work and is oriented towards a polarity model closer to physiological conditions (3D culture technology) and accentuating the efforts of defining the role of EFA6/Arf6 in tumoral progression. The goal is to determine the molecular mechanisms underlying membrane remodeling and actin cytoskeleton reorganization by EFA6/Arf6 proteins and their partner proteins. The project is well-defined. The group expects to obtain continuing funding from ANR and Cancéropole. It has voluntarily restricted its collaborative work to focus on a limited number of subtasks. This increased focus is important for their future success.
In summary, the group is productive, with very good progress in the past 4 years, resulting in several medium impact and one high impact publications. Importantly, the impact and recognition of the group are increasing. The complementary expertise of the two co-leaders on ARF GTPases and epithelial cell biology is a strength of the group. The focus on ubiquitination is leading to increasingly good projects and results.

- Conclusion :

  - Summary

A productive group, with good progress in the past 4 years. Several medium impact and one high impact publications. Focus on ubiquitination appears to be leading to increasingly good projects and results.

  - Strengths and opportunities

-Leaders with complementary expertise in biochemistry of G proteins and cell biology of the epithelium
-Strong key collaborations
-The project opens new opportunities for extension in various aspects of epithelial polarity and cancer. This group is an important component of a growing interest on epithelial cell biology and pathology in the Institute (together with Team E019 and Team E02), which constitutes both a strength and an opportunity.

  - Weaknesses and threats

- Low attractivity for PhD students
- Need to broaden funding via other sources (ANR, European projects)

  - Recommendations

This group can be a catalist of epithelial cell biology in the Institute. It should aim to develop strategies to attract new students and to broaden its funding sources. Its international visibility could be improved.

- **E8 Development of Innovative Therapeutical Strategies for Depression and Stroke Treatment**
- **Team Leader Catherine HEURTEAUX**
- **Staff members (on the basis of the application file submitted to the AERES)**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	2	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1,8	1,8
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	
N7: Number of staff members with a HDR or a similar grade	1	2

- Appreciation on the results

The group is independent since 2007, as one of the 3 teams originating from the Lazdunski's team. There is therefore a one year overlap with the results obtained in the original team. However, even considering the results published from 2007, the quality, relevance and originality of the research appear very good and of high impact. The work has been centered around TREK-1, a potassium channel in the CNS. At the molecular level, the group has various tools to investigate its function, including KO mice. Furthermore they study Alpha-linolenic acid (ALA), the channel activator and spadin (neurotensin receptor, NTSR3 propeptide) as a blocker. The group have also approached traditional chinese medicines (TCMs) and, in addition, used Psalmotoxin 1 from a tarantula. The have also identified (with another IPMC team) NTSR3 as a TREK-1 partner. Those tools are employed to address various disease conditions, such as stroke, pain, and depression. This set of studies is original, well advanced and timely.
The total number of publications in peer-reviewed journals (19 publications, 15 from 2007 including 3 reviews, in 9 out of 15 members of the team are in prominent position including 1 review) appears very good. The major publications since establishment of the group independence, i.e., 2007 are in PLoS Biol and Neuropsychopharmacology which on the top of a number of other publications, including the works led by the previous group leader and published in e.g., Nat Neurosci and EMBO J shows very good level.
Regarding collaborations, most of the papers are collaborative. There are extensive collaborative links both in France and abroad.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

This group has very good links with national, international and local partners and very good international visibility. The group has developed original tool and capitalizes on pathological models developed by others.
There are a number of invitations to international conferences and symposia as well as awards, clearly showing appreciation of the work carried out by the group.
The ability to recruit post-docs and students, and more particularly from abroad, looks appropriate, especially in comparison with several other groups at IPMC.
The financial situation seems very good with sources coming both from academia and industry, although lack of substantial international funds appears visible
The participation to international scientific networks could be improved, there is a big potential to be a partner in international consortia.

Besides publication record, the industrial support already proves socio-economic partnerships and importance of the work for the society and economy. The major diseases tackled (depression and stroke) are of extreme socio-economical importance.

- Appreciation on the strategy, management and life of the team

The team is split into three subgroups, focused on specific areas of research, in what sounds like a good strategy with good team organization. There is a clear teaching component.

- Appreciation on the project

The long term project which aims at the development of innovative therapeutical strategies for depression and stroke treatment is very original, innovative and of great relevance, particularly the part aiming at developing spadin as a new generation of antidepressants targeting the TREK-1 channel and the preclinical validation of the traditional Chinese medicine NeuroAid against cerebrovascular diseases.
The project sounds well thought and very broadly designed as far as the disease targets are concerned, nevertheless focused on specific molecular targets such as spadin, specific TCMs, ALA. Those lines of the proposed research seem to be natural developments for the group. A potential danger is limited expertise in pathophysiological aspects of the proposed work.
The policy for the allocation of resources sounds appropriate. The projects are quite original as focused on available, unique resources. They are considered as mainstream projects as far as an application of those resources is concerned. This sounds like a valid, acceptable, though not ground-breaking strategy.

- Conclusion :

  - Summary

The overall impression is positive. Relevance and originality of both the already performed and the planned research on in vivo function of TREK-1 in relation to stroke and depression and on the development of innovative therapeutic strategies for the treatment of these two major pathologies appear very good.

  - Strengths and opportunities

Main strengths of the team: the recognized expertise, the high number of local, national and international collaborations, the high therapeutic potential of the translational projects, the creation of the animex platform at IPMC. Foundation of the project is based on the discovery made in the Institute. This makes the groups unique and allows seeking appropriate collaborations. The group is well organized.

  - Weaknesses and threats

A bit poor appreciation of the intricacy of the pathophysiological problems to be approached

  - Recommendations

Be ambitious and pursue the big potential to be a partner in international consortia.

- **E9 The polycystin complex: mechanotransduction and intracellular calcium homeostasis**
- **Team Leader Eric HONORE**
- **Staff members (on the basis of the application file submitted to the AERES)**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	5	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	1	
N6: Number of Ph.D. students (Form 2.7 of the application file)	0	
N7: Number of staff members with a HDR or a similar grade	2	3

- Appreciation on the results

During the period 2006-2010, the team shifted its research interest from the traditional K2P channels and their mechanosensitivity to the polycystin complex TRPP1/TRPP2 and the mechanisms mediating its contribution to cellular mechanosensitivity. In this relatively new research topic, the team obtained highly relevant and original results, by providing the first demonstration of a role of polycystins (in particular the TRPP1/TRPP2 dosage) in sensing the pressure in blood vessels through their regulation of stretch-activated ion channels (SACs); various TRPP2 interacting proteins were identified using a proteomic strategy, including the actin crosslinking protein filaminA, which was shown to be critically required for SAC regulation by polycystins. The publication in Cell (2009) of these findings point to their excellent quality and impact.
In the past 5 years, this team published 10 original research papers and 13 review articles. On 4 of the research articles, a member of the team was first and/or last author. On 11 of the 13 review articles, a member of the team was first and/or last author. Of special notice are the research papers in PNAS 2006 and Cell 2009, as well as the 2 review articles in Nature reviews and 1 in Trends in Cardiovascular Medicine. Collaborations are not explicitely mentioned, but judging from the publications, some collaborations have been fruitful over the past years.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The PI has been Chairman of the prestigious Gordon research conferences on Mechano-transduction 2007-2009, and recipient of 5 national prizes in the past 5 years. The team leader was invited speaker at multiple international venues among which the Gordon research conference on cellular osmoregulation. The international visibility of the team is excellent judging from the number of invitations to international conferences and symposia.
The ability to recruit post-docs and students, from abroad is good. The team consists of 3 cnrs/inserm researchers besides dr Honoré. Currently, there are 3 postdocs and there have been 3 postdocs in the past, some of which were from abroad. The team has a good ability to raise competitive international fundings. an excellent ability to raise funds from national sources. The team raised 2 M€ worth of grants. Of the 17 grants some are from competitive institutes such as Marie Curie and HFSP. Most grant money comes from ANR (580 k€). There is a good participation in international networks.

- Appreciation on the project

The long term scientific project builds on the very original results published in Cell 09 and aims at investigating the role of the molecular partner of TRPP2 filaminA in arterial mechanotransduction and the role of TRPP2 in combination with a previously identified partner in intracellular calcium homeostasis. The aims appear very relevant, original and in general feasible. However, the feasibility might depend also on the ability to increase workforce. Projects all have the potential to yield cutting edge results.

- Conclusion :

  - Summary

This is a strong team. Relevance and originality of both the already performed and the planned research on the role of TRPP2 in combination with its partners in the regulation of arterial mechanotransduction and intracellular calcium homeostasis appear excellent or very good. The main strengths of the team appear the originality, the very good funding and good links with international networks.

  - Strengths and opportunities

Creativity. High quality research. Very relevant and original research lines. Opportunity to interact with team 01.

  - Weaknesses and threats

Size of the team (and possibly the present expertise) might be not adequate, given the large number of interesting projects. Many reviews, but less primary research articles.
Few collaborations locally, but also at the european level.

  - Recommendations

Increase team size or refocus. Balance between number of reviews and primary research articles should shift towards more primary research. Invest more in local collaborations, especially with team 1.

- **E10 Mechanisms of gene regulation in physiopathology**
- **Team Leader Enzo LALLI**
- **Staff members (on the basis of the application file submitted to the AERES)**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	
N6: Number of Ph.D. students (Form 2.7 of the application file)	0	
N7: Number of staff members with a HDR or a similar grade	2	2

- Appreciation on the results

The research activities of this team are focused on the role of SF-1 (the nuclear receptor stereoigenic factor-1) dosage in the pathogenesis of adrenocortical tumors and development of therapeutic strategies, including precilical trials using novel drugs targeting beta-cathenin pathway (inhibitors of beta-cathenin), SF-1 inverse agonists and MTOR inhibitors. The team is also investigating the role of transcription factor Dax-1 in mouse embryonic stem cells and in the pathogeny of Ewing tumors in human, and the role of the Task1 potassium channel in regulating functional zonation of the adenal cortex. The research performed seems solid, but not particularly innovative or exciting.

The research activities of this team led to contributions in 27 publications (between 2006 and 2010), and 5 reviews, which is about 2 publications per researcher per year, above average. The publications are in general not in high profile journals, but some are reasonably well cited.

Several collaborations exist with international partners. The partnerships are steady, generating publications over several years.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The PI received an award from the academy of science. He is frequently invited to talk, in particular in international events.

The group is of a reasonable size, the number of full time researchers is high. The recruitment of a new researcher somehow can be seen as a success, although it is not clear at all how she fits in the themes of the group.

The group raised about 1 M Euros in 4 years, from various sources including international ones. The PI coordinates several research projects, including international ones.

- Appreciation on the project

The proposed project is in continuation with previous work. It includes analysis of mechanisms of transcriptional regulation by SF-1 and DAX-1, preclinical studies of novel drugs on tumor cells. Research activities are also extended to the role of TASK potassium channels in adrenal function zonation and pathophysiology of hypertension, and study of the relation ship between gene expression and mechanical stress. It would not be a problem if the current research was cutting edge or on the forefront. As it stands and in view of the previous results and contribution, the proposed project appears conventional with no real originality. It is also difficult to expect significant breakthroughs from the proposed investigations. Translational part of the project may appear potentially interesting. However, it is not clear why the PI and his team want to pursue these investigations. The choice concerning new projects is also not well justified, including its integration to the other projects. The project developed by the new researcher, concerning the regulation of gene expression by mechanical stress in cardiomyocyte, is completely disconnected from the rest of the group. Although we understand the reasons of her arrival, it should be made sure it is a strength and not a cause of unfocusing.

- Conclusion :

  - Summary

This team has a good past scientific production relating to pathogenesis of adrenocortical tumors and transcription factors. The projects are however a bit unfocussed and not very enthousiastic in view of the international competition.

  - Strengths and opportunities

Good expertise in the field of adrenocortical tumors. Good scientific production (quantitatively). Diverse collaborations.

  - Weaknesses and threats

Dispersion. There is a lack of sharpness in identifying the major research questions

  - Recommendations

The team should focus the project on the group's field of expertise and make a better use of IPMC facilities to be more ambitions and broaden the approaches used. Past activity justifies trusting the continuation of the group activity but the panel was not very enthusiastic with the projects proposed in term of long term competitiveness and pertinence. The translational part of the project may appear potentially interesting. However, it is not clear why the PI and his team want to pursue these investigations.

- **E11 Molecular physiopathology of phospholipases A2 and their mediators**
- **Team Leader Gérard LAMBEAU**
- **Staff members (on the basis of the application file submitted to the AERES)**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	4	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	
N6: Number of Ph.D. students (Form 2.7 of the application file)	0	
N7: Number of staff members with a HDR or a similar grade	2	2

- Appreciation on the results

The E11 team (Molecular physiopathology of phospholipases A2 and their mediators) works on the structure, function and mechanism of action of secreted phospholipases A2.The team has a long-standing expertise in the sPLA2 field since about twenty years. The challenge here is to identify the biological functions of mammalian sPLA2s and their receptors in normal and physiopathological conditions. The team has developped unique molecular tools, especially in biochemistry and molecular biology.
The quality and impact of the research results is very high and is acknowledged by a large number of publications in good to high impact factor journals (*New England J of Medicine, EMBO reports, British J of Cancer,FASEB J, J. Biol. Chem…),* invitations at conferences (8 in total over the past period) and of review articles (Annual Review of Biochemistry, Circulation). In addition, the results have also an impact on a more applied point of view (6 patents filed in the past 2 years).

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team has established a very good network of local, national and international collaborators (including Harvard Medical School in Boston and Tokyo). The funding of the team originates from multiple sources, including ARC, ANR, CNRS-JSPS joint program and a contract with a start-up company.
Two CNRS researchers have joined the group within the past four years, one with a strong expertise in structural biochemistry and drug design, but there is no assistant professor in the group. However, the team leader is involved in several teaching activities in France but also abroad.

- Appreciation on the project

The project is based on the previous and recent results obtained by the group in the field of PLA2. It is composed of six major subprojects, each focusing on the specific role of sPLA2 and lipid mediators in one area (fertility, atherosclerosis, host defense, cellular senescence and cancer,...). For each sub-project, the expected source of funding, the people involved in each subproject and the valorization objectives are clearly described. The potential for a valorization of the results is high as sPLA2 can potentially be employed as a novel therapeutic target.

- Conclusion

  - Strengths and opportunities

- Long experience in the PLA2 field, development of unique molecular tools (recombinant proteins, specific antibodies and method of detection) and technological skills, especially in biochemistry and molecular biology
- Production of high quality and strong French and international collaborations
- Recent recruitment of new lab members
- sPLA2 as possible novel biotherapeutic molecules and biomarkers of disease

  - Weaknesses and threats

- Need for external expertise to analyze the diversity of sPLA2 functions
- Relatively small team

  - Recommendations

The team is encouraged to pursue his efforts for increasing its size, by recruiting students (PhD, post-doctoral researchers). The exploration of the role of sPLA2s as a biomarker of disease and as novel biotherapeutic molecules should also be strengthened.

- **E12 Molecular Physiology and Physiopathology of Ion Channels**
- **Team Leader Florian LESAGE**
- **Staff members (on the basis of the application file submitted to the AERES)**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	4
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	
N7: Number of staff members with a HDR or a similar grade	1	1

- Appreciation on the results

The team studies the composition and physiological role of native brain K2p channels and investigates their role in neuronal disorders. The quality, relevance and originality of the research on the composition of native brain K2p channels and their physiological role appear very good. The research program aimed at examining the involvement of K2p channels in idiopathic epilepsy has been stopped due to the negative results (but this is anyway relevant).
Over the past 4 years the team published 8 original research papers, of which 6 with the PI as senior author, and 3 review papers (with the PI as senior author). Although modest in number, the quality of the papers is very high to excellent: 1x Cell, 2x PNAS, 2x EMBO J, 2x JNeurosci. The number of citations the publications receive is relatively modest; for instance the Cell paper from 2007 yielded 19 citations thus far.
The collaborative projects with collaborators outside IPMC yielded two high quality publications in PNAS and EMBO J.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team received several prizes and awards. The PI is on 5 editorial boards and gave 5 invited talks in the past 4 years.
The team does not comprise post-docs and/or students from abroad. In addition to the team leader, the team consists of 2 more researchers from Inserm and CNRS. No postdocs, 2 present PhD students and 1 past PhD student.
Funds raised in the past 4 years is relatively modest. 3 grants totalling 323 k€ and 1 grant raised in 2004 are listed. No funds from international sources.
The PI has been the organizer and chair of a symposium at the 37th IUPS meeting 2009 in Japan. Collaboration with foreign partners is limited, but a recently established collaboration with a team of Univ of Berkeley (California) appears very fruitful.
In addition to the scientific research papers, the PI has filed 5 international patents.

- Appreciation on the strategy, management and life of the team

The team consists of 3 inserm/cnrs researchers, an engineer and 2 PhD students. The team lacks postdocs. Senior members may be a bit overrepresented compared to junior members.
Two researchers have spent time on teaching, total 237 hrs.

- Appreciation on the project

The long term project that will continue to explore the molecular physiology of K2p channels appears relevant and in general feasible given the previous performance of the team. The majority of the projects outlined for the coming 4 years are logical follow ups of the existing research lines, and appear feasible. Some interesting new fluorescent methods (recently acquired by one of the researcher) will be used to investigate TREK subunit multimerization and TWIK trafficking, and have been used to obtain a light-switchable TREK channel, that open new interesting research avenues. The rationale and the feasibility of the project on acquired channelopathies are not entirely clear. The projects on the KO mice are important extensions of the research lines that will facilitate high impact output. Although these projects rely more on outside collaborations, the projects are still feasible. The team may wish to explore potential in house collaborations for KO mice phenotyping.Some projects (in collaboration with Berkeley) are excellent, and hold high impact potential.
The projects on the KO mice and the light-switchable TREK channels are original and will most likely yield interesting results with high impact.

- Conclusion :

  - Summary

The team has produced high quality and excellent research output, even though the number of papers could be higher given that 3 inserm/cnrs researchers were present in the team. The external research funding is modest and should increase, especially since a 4th researcher will join the team. Relevance and originality of both the already performed and the planned research on the molecular physiology of K2p channels appear in general very good. The future projects on KO mice and light-switchable TREK channel are interesting and worthwhile pursuing.

  - Strengths and opportunities

Main strength of the team: the strong backbone of permanent researchers with a broad range of expertise, including some newly acquired interesting methods (thanks to the collaboration with a leading team in Berkeley) that have led to new excellent projects with great potential. Good visibility.The team could benefit from local collaborations on systems and behavioral level of analysis.

  - Weaknesses and threats

The number of papers could be higher given that 3 inserm/cnrs researchers were present in the team.
No conclusive results about physiological relevance of channels and mechanisms. The required budget for single molecule imaging at IPMC is not secured yet. Behavioral phenotyping of KO mice relies on outside collaborations.

  - Recommendations

All Inserm/cnrs resaerchers should spend a significant amount of time on acquiring funding. Get help/feedback from senior members of the institute that have been successful in acquiring large grants.
More participation in European networks to apply for european funding. The team may wish to explore potential local collaborations for KO mice phenotyping.

- **E13 Ion Channels and Pain**
- **Team Leader Eric LINGUEGLIA**
- **Staff members (on the basis of the application file submitted to the AERES)**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	4	4
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1,6	1,6
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	
N6: Number of Ph.D. students (Form 2.7 of the application file)	0	
N7: Number of staff members with a HDR or a similar grade	2	3

- Appreciation on the results

The team was created in 2007 (as one of the 3 teams originating from the Lazdunski's lab). Since then the team has been working on ion channels involved in pain. Particular attention is given to acid sensing ion channels (ASICs), which have been first cloned and characterized by the former head of the lab Dr. Lasdunski. The function of these channels are characterized by using pharmacological inhibitors (toxins), knockout mouse models and silencing stragegies. There is a one year overlap with the results obtained in the original Lazdunski lab. However, even considering the results published from 2007, the quality, relevance and originality of the research on the role of ASICs and K2p channels in pain pathways appear very good and of high impact (judging from a few excellent publications, the number of citations they received and the number of inivitations to present the data at international meetings).
The total number of publications in peer-reviewed journals (18 publications, 13 from 2007 including 4 reviews, in 9 out of 13 members of the team are in prominent position including 4 reviews) appears good, especially if one considers the quality of the publications with original results that is in general very high (and in some cases excellent, as in the case of EMBOJ08 showing for the first time that peripheral ASIC3-containing channels are essential sensors of acidic pain and respond synergistically to 3 different inflammatory signals and EMBOJ09 showing that TREK1 and TRAAK channels are important regulators of nociceptor activation by cold, particularly in the population that is not activated by menthol).
Other outputs : 2 patents filed (2008, 2010).
Collaboration with other French labs specialized in the pathophysiology of pain.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The international visibility of the team is good judging from the number of invitations to international conferences and symposia: 12 invitations to national and international meetings (8 by the group leader, 4 by other members of the group).
In contrast, the capacity to attract post-docs and students during the last 4 years is weak (5 graduates students and 0 post-doc during this time).
Overall funding situation in the past was good (several contracts from ANR, AFM). Current funding could be improved (most funding appears to end by 2011). The team does not appear leader of major contracts at the moment and does not participate in international scientific clusters (EU projects etc.). The team seems to be only involved in national collaborations, which are however complementary and quite successful. There are joint publications with collaborators, 2 patents filed on toxins.

- Appreciation on the project

The proposed project is divided into three topics : 1) Pharmacology of ASIC and K2P channels, 2) ASIC and pain, 3) Contribution of K2P channels to pain and to the effects of morphine. The long term project appears very relevant and in general feasible given the previous performance of the team. Particularly relevant appears the plan to investigate the role of ASICs in animal models of different pain conditions including post-operative pain, visceral pain and bone cancer pain, which will combine molecular, electrophysiological and behavioural studies. The plan to investigate the role of ASIC in synaptic transmission and plasticity in the spinal cord is certainly relevant, but it is not clear whether the skills to perform electrophysiological recordings in vivo and in spinal cord slices are present in the team, and how the team plans to develop them.
The human resources are very comfortable with 4 full time permanent researchers and 1 professor as well as to expert technicials with permanent positions. A raisonable amount of funding has been raised, which could however be improved.

- Conclusion:

  - Summary

This team is specialized on ion channels involved in pain with particular attention given to acid sensing ion channels (ASICs) with a good scientific production. The scientific leadership and attractivity could however be improved.

  - Strengths and opportunities

Team emerging from the former Lazundski lab with a long history, a lot of expertise and permanent researches and technicians. Very solide and straight forward project. The main strengths of the team appear the strong backbone of permanent researchers with a broad range of expertise (including some unique high-skill techniques such as nerve-skin preparation and long term expertise in animal toxins and ion channels) and the good links with national scientific networks. Identification of peptide toxins with analgesic effect may lead to development of effective industrial partnership.

  - Weaknesses and threats

Publications are still co-signed by the former lab director (Dr. Lazdunski), which might question the leadership of the current team leader. No post-docs and only very few PhD students attracted during the last 4 years. Funding could become a problem. The team may lack sufficient expertise in spinal cord in vivo and slice recordings. The increasing number of planned in vivo approaches are important but might be a threat.

  - Recommendations

Improve your attractivness and visibility. Need to improve the ability to recruit students and post-docs and need to raise funds for the long term project. Become coordinator of major grants (ANR, CE, etc.). Strengthen the partnership with the spin-off company Teralpha.

- **E14 Molecular and Cellular Pathophysiology of Voltage-Gated Na+ channels and Neuronal Excitability**
- **Massimo MANTEGAZZA**
- **Staff members (on the basis of the application file submitted to the AERES)**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	0
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	
N7: Number of staff members with a HDR or a similar grade	0	1

- Appreciation on the results

The team is one of those recently recruited and has been present for only 1 year, hence impossible to evaluate for the performance in a new location. However, in the previous 4 years the team (working at the Besta Institute in Milano) was quite productive; the results on the functional consequences of NaV1.1 mutations causing epilepsy or migraine were well published and original; they provide the right foundation for the proposed research.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

Good international collaborative links indicate attractiveness at this level. Given the recent move to France from Italy, the links with national partners and national funding appear still limited. The invitations to international conferences and symposia looks very good. The ability to recruit students looks OK: 1 PhD 1 MSc. The participation to international or national scientific networks is very good with one FP EU grant.
Epilepsy is a very important disease of socio-economic importance, Hence the proposed research may have significant economical implications

- Appreciation on the project

The long term project appears very relevant and innovative. The project regarding the study of the functional role of neuronal Na+ channels and the effect of their pathogenic mutations, together with structure/function studies of sodium channels and toxins appear quite feasible given the previous performance of the team. The feasibility of the proposed innovative approach to rescue folding defective mutant channels and of the viral delivery approach for selective modulation of the function of different neuron subtypes is less clear due to the lack of preliminary findings. However, overall there is a good balance of risk-taking and safe projects.

- Conclusion :

  - Summary

The overall impression is positive. Relevance and originality of both the already performed and the planned research on the pathophysiology of voltage-gated Na+ channels and neuronal excitability appear very good.

- Strengths and opportunities

Well defined goals, based on the previous achievements. Societal/medical Importance of the topic. Internationally recognized expertise in the functional analysis of Na+ channels, in epileptogenic channelopathies and peptidic toxins; many good international collaborations including close contacts with clinicial and medical geneticists. Opportunities to use proteomics core facilities and take advantage of the expertise of the Institute in toxins.

- Weaknesses and threats

Small team (considering the many ambitious projects). Limited use of the internal resources, including lack of effective collaborations

- Recommendations

Be more interactive locally. Recruit expert post-docs

- **E15 Activity dependent dynamics and roles of synaptic sumoylation**
- **Team Leader Stéphane MARTIN**
- **Staff members (on the basis of the application file submitted to the AERES)**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	0,8
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	
N6: Number of Ph.D. students (Form 2.7 of the application file)	0	
N7: Number of staff members with a HDR or a similar grade	0	2

- Appreciation on the results

This is a new group that was formed in November 2008 with the support of a 3 year ATIP CNRS grant. The PI was also awarded a meritorious Royal Society University Fellowship to establish his laboratory in England but did not accept it. The PI had a very successful postdoctoral stay from 2006 to 2008 at the MRC center for synaptic plasticity (Bristol, UK). During this time, he discovered an important role of sumoylation in the regulation of synaptic transmission by kainate receptors.
The team leader published several high impact publications during his postdoctoral stay, including first author papers in Nature and second author papers in Neuron and Nature Cell Biology and a first author review in Nature Neuroscience. A collaborative publication in PLOS one is listed on a subject not directly related to the focus of the laboratory.
Other outputs : Training of 1 PhD student, was invited at 3 occasions (national and international workshops)
A collaboration has been kept with the MRC laboratory. There seems to be an agreement on the splitting on the sumoylation theme with the original laboratory

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The group is still very young. The PI was invited to an IBRO international workshop in 2010 (Hungary) and in 2009 to an INSERM workshop in St Raphael, France.
Due to the ATIP grant 1 post-doc was hired. Another CR1 researcher joined the team. Although the team is still small, the dynamic is positive.
The main funding for the laboratory is the ATIP young investigator award (300kE) from the CNRS (2008-11), which may be extended by two years, a FRC grant (30 kE) from FRC to study sumoylation substrates during brain development and an equipment grant (75 kE) from FRC (2009). The team does not participate yet in scientific clusters (EU projects etc.)
International collaborations with the former mentor and a collaboration with the Max Planck Institute, Goettingen, Germany on SUMO transgenic mouse models.

- Appreciation on the strategy, management and life of the team

This is a young group that appears to be taking off with some recruitment and some interesting results. The team participates to improve the scientific environment (microscope equipment).

- Appreciation on the project

During the two years since its inception, the laboratory has focused on three projects, (i) the trafficking of sumoylation enzymes in hypocampal neurons, (ii) identification and functional characterization of sumoylation substrates in developmental brain and (iii) roles of sumoylation in Prion disease.
Project is potentially innovative. Some interesting sumoylation substrates were identified by the PI; they appear to be "interesting proteins, related to disease". Trafficking of sumoylation enzymes is a major goal; however, a general hypothesis on possible mechanisms was not presented.
The human resources are increasing with the arrival of another CR researcher, funding has been obtained until 2011. Preliminary results have been accumulated underlining the feasability of the projects. Topic three, role of sumoylation in Prion disease, will be conducted in collaboration with team E5 at the IPMC.

- Conclusion :

  - Summary

A young group, too early to provide a clear evaluation of results. Relative little preliminary data for a 2 year period.

  - Strengths and opportunities

The study of the role of sumoylation synaptic transmission and brain development is timely and could have significant impact. Young and dynamic group with highly original project. Team leader has shown its capacity to obtain funding and to attract progressively new collaborators.

  - Weaknesses and threats

A weakness is the short term funding young investigator award (3 years) and the lack of students in the laboratory. No publications since the establishment of the team in 2008. Presented preliminary results are not clear.

  - Recommendations

Young and promissing team. Publication of accumulated results is recommanded and the preparation of the transition when the ATIP grant will finish (2011).

- **E16 Cellular biology of neuropeptides and associated pathologies**
- **Team Leader Jean MAZELLA**
- **Staff members (on the basis of the application file submitted to the AERES)**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	0
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	
N7: Number of staff members with a HDR or a similar grade	3	2

- Appreciation on the results

The lab has been created in 2007. The work focuses on neurotensin (NT) and its receptors, especially NTSR3. Those are studied in a variety of systems, ranging from pancreas to brain to tumors. The results displayed in the report seem of significant relevance with expected great impact; in fact, these results provide evidence for unforeseen roles of neurotensin in the control of depression and to a lesser extent diabetes, 2 major health problems. Although the quality of undertaken studies are good, they cannot be ranked as top quality studies.
The group has a good track record of publications, with a prominent collaborative publication on depression; the other papers are at the medium level. The number of post-docs and PhD students seems surprisingly low for the number of staff members, which might result from the group's efforts to support undergraduate training (albeit this is seldom a rewarding strategy).
The group seems to have a remarkable facility in establishing partnership at different levels: 1) they established a solid intra-mural scientific partnership; 2) they are actively involved in management of services at their Institute (administrative partnerships); 3) they have collaborations with chemistry groups in the US (inter-disciplinary partnerships); 4) they have partnerships with a pharmaceutical company (private-academic partnerships); 5) they seem to dedicate time and interest to the support of undergraduate training (academic-research partnerships). This pleotropic activity should be highlighted.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The group seems to have a limited visibility in the international arena, with few invitations to international conferences and symposia. This is surprising in view of the emerging novelty and potential interest of their recent research.
The number of post-docs and PhD students is surprisingly low in view of the number of staff members. The group is an example of a reverse pyramide. Most of the researchers are well advanced in the carreer.
The track record of fund raising is rather disappointing. The group seems to have secured its immediate future, with a combination of private money (not specified) and public funds. However, it is a mystery how the group could have survived with 16 k€ in the last 5 years. There seems to be a major need to broaden the scope of possible targets for funding. In spite of this recognised difficulty in raising funds, the group has established what seems to be solid and relevant partnerships, both with different pluri-disciplinary research groups, as well as with industrial partners.
The report does not mention any involvement in scientific network. But, as mentioned above, the group has established some stable partnerships/ collaborations with national and foreign groups.

The group has been able to build 2 clear hypothesis for intervention based on NT-related peptides, which are novel. They are developing novel candidate ligands (collaboration with a chemistry group), gauge their stability (own planned work) and have the tools to carry out the translational work, through their partnership with a pharma.

- Appreciation on the strategy, management and life of the team

The group presented a well-defined and ambitious plan of activities; the novelty of some of the questions and the solidity and rationale of the established partnerships clearly indicate that the group is following a promising project in years to come.
The participation in formal teaching is mentioned in the report, especially the commitment to participate in undergraduate training. This aspect is not detailed in the scientific report, albeit it is mentioned to be time-consuming.

- Appreciation on the project

The presented project is solid and ambitious and its feasibility is sustained by both the previous results obtained, the group's expertise and the established partnerships.
The resources seem to be available to carry out the project, albeit the manpower seems limited. These studies should provide useful, although not groundbreaking results.

- Conclusion :

  - Summary

It seems that in the last years the group was able to establish the foundations (science and partnerships) and generated a new tool (spadin) that seems worth exploring the physiopathological roles. Whether the group has the man power and attractibility (students and funding) to develop the proposed workplan is an open question.

  - Strengths and opportunities

The group has devised an interesting tool (spadin) and rose two working hypothesis (role in depression and role as a retrograde messenger between insulin targets and producing cells).

  - Weaknesses and threats

The proof of concept supporting the two main projects is still weak: spadin modified mice's behavior, but was not shown to be an anti-depressive; also, spadin affects pancreatic beta-cell responses, but the relevance of this finding is unclear. Also, the chemistry improvement and the pharmaco-kinetic studies are very manpower consuming and new in terms of methodology to the group. The group should also be more 'aggressive' to recruit more students (2 trainees, i.e. PhD or post-docs, seems too limited) and raise funds. For this to happen, the group needs to increase its international visibility.

  - Recommendations

As, expressed above, there is the clear need to enhance the group's manpower and its funding. Increasing the manpower is partly the groups' responsibility (i.e attracting top students) and partly institutional (a technician should be recruited for the group). Certainly the funding is the groups' responsibility and the group seems to have all that is required to raise funds at the international level.

- **E17 Genomics and Evolution in Neuro-Endocrinology (GENE)**
- **Team Leader Jean-Louis NAHON**
- **Staff members (on the basis of the application file submitted to the AERES)**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	3	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	0
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	2	
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	
N7: Number of staff members with a HDR or a similar grade	2	2

- Appreciation on the results

This team is working on three different research lines, one is on regulation of neuroendocrine (MCHRs) functions; one is neuroinflammation in relation to feeding behavior and energy balance; the last is genomics and evolution, especially on the structure and expression of the "primate specific" genes. The projects contain some originality, especially to the primate specific genes. But impacts of results may be higher to other two projects if successful. Some results are surprising and promising, such as the regulation of trans-spliced non-coding RNAs.

The output of the team is moderate. There is less than a publication per researcher per year, and only 13 are signed in leading or senior positions. The general quality of the publications is moderate, with one paper in *Journal of Neuroscience*. Two researchers have been invited to international conferences.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The recruitment seems to be low, maybe due to limited funding with no attraction of international members.

The track record of fund raising is good. Several grants have been obtained over the period, including funding from EU. However two of the three big grants have been obtained in collaboration. It is not clear that they reflect the ability of the PI to raise money. One patent has been filed.

- Appreciation on the project

The willingness to merge the different trends of the team's research should be encouraged. However, this is not really visible past the introduction. For the next 4 years, even more diverse and ambitious projects have been presented. They cover function assessment of primate chimeric gene transcripts from PMCHL1/2 genes; PMCHL ncRNA and MCH signaling in cilia development and neuroendocrine functions; in primate Parkinson models and finally chemokines and neuropeptides in the central control of deeding behavior and energy balance. The team is a medium-sized group with 4 scientists and 1 technical staff now, and expect to recruit 3 more staffs in the next 4 years.

The projet on "trans-splicing" between exons coming from the two strands (or swapping exons) is exciting and cutting-edge. But it is peripheral to the main project of the group.

- Conclusion :

  - Summary

This is one of the founding teams of the institute with a past record of excellent and original contributions. However, the more recent activity has been less prominent, maybe due to too much diversity in the projects.

  - Strengths and opportunities

The strength is that the team seems to be having the know-how on the proposed projects, which are also original.

  - Weaknesses and threats

There are several weaknesses in the projects. Mainly, the project is too diverse, unfocused and ambitious. The mechanism for general allocation of ressources is unclear. With the current funding and manpower, the committee has doubts that the group can accomplish all the experiments proposed. The team has to set their priority when the funding and manpower are limited.

  - Recommendations

Refocussing of the team and adapting the goals to the ressources is encouraged. Technical support would certainly help.

- **E18 Molecular mechanisms of neuronal plasticity in health and disease**
- **Team Leader Hélène MARIE**
- **Staff members (on the basis of the application file submitted to the AERES)**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	0	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0	2
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	0
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	
N6: Number of Ph.D. students (Form 2.7 of the application file)	0	
N7: Number of staff members with a HDR or a similar grade	0	1

- Appreciation on the results

The team started only very recently at IPMC (Oct 1, 2010). This team studies molecular mechanisms underlying neuronal plasticity and memory formation in rodents. In addition, the PI studies how these mechanisms become defective in disease and tests novel therapeutic approaches. These are very relevant and central topics in neurosciences to which the PI takes an original approach. The team leader's activity in the last years has been of high quality, as testified by her list of publications. She has strongly contributed to bringing the topic of synaptic dysfucntion to neuro-psychiatric diseases, using a robust merging of viral-mediated genetic manipulations with fine electrophysiological analysis. In this sense, her past research is certainly original and of relevance and has had reasonably strong impact.

In 2009 and 2010, the PI published 4 first/last author papers (J Neurosci, Biological Psychiatry, Frontiers in Cellular Neuroscience, Hippocampus) of high quality. In particular the findings in the J Neurosci and Biological Psychiatry papers are very relevant and will have good impact in the field. Publications in high impact journals with the PI as senior author are still to come, but we are confident that that will happen in the near future. In addition, the number of trainees is still mosdest, but expected to raise exponentially in the forthcoming years.

The group leader's scientific robustness and rather unique expertise has enable her to establish strong and long-lasting partnerships in all places where she has worked: first in the US, then in Rome and very likely now at IPMC, with her newly identified prime collaborator. The collaborations are very successful. The PI co-authored 2 Neuron papers in 2009 with formers members of the lab where the group leader spent her postdoctoral years. In addition, the PI co-authored a Nature Neuroscience paper in January 2011, with former colleagues at the EBRI in Italy where she worked prior to arriving at IPMC. These collaborators also contributed to the papers on which the PI is senior author.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The PI is young investigator at the prestigious ENI-Net network (gathering some of the most promising European neuroscientists) and received a NARSAD young investigator award, reflecting the excellence of postdoctoral work. In spite of working in a very competitive field, the team leader is regularly invited to conferences and symposia: 4 invitations as a speaker at 4 events in 2008 and 2009, among which 2 ENI-Net meetings.

The past record shows a surprisingly modest ability to recruit high quality students and researchers to her group, which is surprisingly in view of the wide interests of the topics approached and the cutting-edge methodologies used. The PI supervised 2 postdocs that published first author papers in 2010, in high quality journals. The PhD student was second author on the 2010 J Neurosci paper.

In the past, the team leader received 5 small sized research grants, roughly totalling to a modest 200 k€. Recently, the PI received an ATIP and a SIT alzheimer grant, which will enable her team to expand.

Her scientific activity has pushed ahead the relevance of synaptic dysfunction in neuro-psychiatric disorders and she contributed for the generation of novel tools for research. However, this has not yet translated into concrete conclusions that one may foresee being exploitable from the socio-economic point of view.

- Appreciation on the strategy, management and life of the team

The PI has headed a small team in Italy, but no people have joined in IPMC. Now 1 postdoc is present, and another is going to be recruited.

The establishment of the group at IPMC seems to have been based on 3 major strategies: 1) development of some of her own's ideas; 2) exploitation of previous collaborations to bolster some novel projects; 3) establishment of a novel partnership with a solid and innovative group at IPMC. Any of these strategies is expected to yield an expected high quality reward.

- Appreciation on the project

The described projects are very relevant and seem feasible within the new setting at the IMPC, albeit some focus and selection might be required.

To test the hypothesis whether microRNAs affect glutamatergic transmission and plasticity is original. Extending the research in both projects to in vivo approaches to test hippocampal function and plasticity is certainly ambitious; in particular using interference and rescue experiments both in vitro and in vivo. However, they mainly constitute important refinements of an established idea, i.e that synaptic function is perturbed in neuro-psychiatric disorders.

- Conclusion :

  - Summary

Clearly a very competent researcher, with a strong past record of achievements and with appealing technical expertise. She combines the scientific winsdom with the personal skills required to smooth her integration at her new Institute, where the activities of some of the groups fully justify her integration. There is now the need to provide real support for her installation and expect that she implements a very pro-active attitude to recruit high quality personel and students and to raise the required funds to support this rather expensive workplan. The team generated a solid output in 2009 and 2010. The output of the international collaborations is excellent, representing a strong network. These results hold great promise for generating excellent output in the coming years. The IPMC is an excellent environment to harbor and foster this team's research.

  - Strengths and opportunities

The main strengths and opportunites lay in the visibility of the research area and the appealing expertise of the group. The new environment at IPMC also offers major opportunities, namely the existence of a very strong and competent group in molecular aspect of neurodegenerative diseases (identified by the PI), but also a group with strong competence in depression, a topic which the committee considers to be an opportunity both scientifically and financially. The PI combines very strong technical approaches in vitro and vivo to test and interfere with hippocampal function and plasticity. Good international network.

  - Weaknesses and threats

The first and main threat is the ability to setup her research lab at IPMC. The second major threat is the rapid erosion of the novelty both of the concepts and of the expertise of the group; in fact, considering synapses as the first and major site of dysfunction for the development of neurological disorders (not so much psychiatric though) is being increasingly accepted and championed by different groups worldwide; also, viral technology is becoming increasingly available. As for the major weaknesses, from the scientific point of view, the main focus on a single brain region may become limiting; from the organization point of view, the group seems to be over-dependent on the PI, i.e. it still lacks a minimal structure in terms of either permanent personel and quality students. Current lack of senior authored high impact papers. Many different projects for a starting team.

  - Recommendations

Since the team is still setting up, a prioritization of projects while postdocs still need to be recruited is necessary. Do not work on all projects at once.

- **E19 Mucosal immunology and inflammation**
- **Team Leader Nicolas GLAICHENHAUS**
- **Staff members (on the basis of the application file submitted to the AERES)**

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	0	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	0	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	0	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	0
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	0	
N6: Number of Ph.D. students (Form 2.7 of the application file)	0	
N7: Number of staff members with a HDR or a similar grade	0	4

- Appreciation on the results

  - Relevance and originality of the research, quality and impact of the results

This is a very active and successful group. Primary projects involved high impact research on immunological mechanisms responsible for asthma and potential therapeutic strategies, mechanisms involved in the priming and differentiation of T-cells in mice infected with Leishmania and Listeria monocitogenes. Secondary projects involve imaging studies on the differential migration of B- and T-cells within lymph nodes and spleen during an immune response and the structural and physiological bases of the role of adenosine deaminases in cancer, using crystallographic and biochemical approaches.

They also have two side projects which are investigating how immune cells move within secondary lymphoid organs and the function of ADA2 in cancer. In the asthma project the team determined the role of CX3CL1 in the disease and found that it plays a critical role by using mice deficient for this chemokine, or by injection blocking mAbs. They showed it is essential for T cell survival. In the second project they have investigated how breast milk transfer of an antigen induces tolerance from allergic asthma by the exposing of lactating mice to an airborne allergen. They found that this is indeed the case and the effect was even stronger if the mother were previously sensitized with the antigen. They have shown that immune complexes are transferred from the mother to the newborn.

In a third project they have demonstrated that oral administration of bacterial extracts prevents asthma via the requirement of T reg cells. In the fourth project they have shown that a single low dose injection of LPS was sufficient to induce airway inflammation in post asthmatic mice. They showed that langerin+ DC are involved in this process.

The group's research has resulted in high impact publications in Nature Medicine (2), PLOS pathog (1), IMMUNITY (1) Mucosal Immunology (2) Cell Microbiology (1) and J Experimental Medicine (2). Presentations have been made at high quality international meetings (including Gordon Conference, Keystone Symposium and EMBO meeting). Very productive collaborations are ongoing.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team is attractive and very well recognized. French Academy of Sciences Award to the PI (2008). Participation in international immunology and Allergy meetings. 2 PhD students completed the thesis and 2 started their theses. All of them are french. Postdoctoral fellows are also french. Two postdocs moved to independent positions in France and USA.

The team is very well funded, with 3 competitive grants from ANR (over 600 kE), from FRM (280 kE), industrial contracts (218 kE), equipment grants (172 (kE), postdoctoral fellowships (4) and predoctoral fellowships (4).

- Appreciation on the project

The project that is planed for the next 5 years deals with Treg cells. The team proposes to use the systems that they have developed to study the role of Treg cells in these systems. It is an exciting project. They plan to investigate the molecular and cellular pathways that are involved in the development of antigen specific Treg in neonates and to identify the signals that control Treg activity in the inflamed tissues. They will test by using KO mice whether various Fc receptors are involved in the induction of tolerance in the breastfeeding-induced tolerance. They will also test whether Fc sialylation is important for the induction of Treg by using various enzymes. Then they will test mainly by using the OVA peptide model, whether DC are responsible for the differentiation of Treg cells.

The second project will be performed in humans and here the group suggests to test whether human milk contains free or IgG-bound antigen and whether they could induce allergen-specific tolerance.

In the next project the team will use the DEREG mice to study Treg cells, they will use siRNA screenings to discover new pathways controlling Treg function. They will use ShRNA system to identify genes that control of Treg activity under inflammatory conditions. Overall the project is original and innovative.

- Conclusion :

  - Summary

This is a strong team with original and innovative research and questions.

  - Strengths and opportunities

Strong team, exciting and innovative research. There is an opportunity in the IPMC of interaction with the epithelium teams.

  - Weaknesses and threats

The team is somewhat isolated in the IPMC. There is little grant money from outside of France. Also it seems as if not all team members contribute equally to the success of the team, i.e. some are publishing more than others.

  - Recommendations

Develop interactions with the other IPMC teams, particularly those working on epithelium.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
INSTITUT DE PHARMACOLOGIE MOLÉCULAIRE ET CELLULAIRE (IPMC)	**A+**	**A+**	**A**	**A**	**A+**
DYNAMICS OF LIPID MEMBRANES AND PROTEIN COATS [BARBRY-ANTONNY]	A+	A+	Non noté	A+	A+
PHYSIOLOGICAL GENOMICS OF EUKARYOTES [BARBRY-BARBRY]	A	A+	Non noté	A	A
PHYSIOPATHOLOGY OF INTELLECTUAL DISABILITY [BARBRY-BARDONI]	A	A+	Non noté	A	A
ROLE AND REGULATION OF NATURAL KILLER CELLS [BARBRY-BRAUD]	A	A	Non noté	A	A
PHYSIOPATHOLOGY OF PRIO DISEASES [BARBRY-CHABRY]	A	B	Non noté	B	B
MOLECULAR AND CELLULAR BIOLOGY OF NORMAL AND PATHOLOGICAL CEREBRAL AGEING [BARBRY-CHECLER]	A+	A+	Non noté	A+	A+
ARF PROTEINS, CELL MORPHOLOGY AND MEMBRANE TRANSPORT [BARBRY-FRANCO-LUTON]	A	A	Non noté	A	A
MUCOSAL IMMUNOLOGY AND INFLAMMATION [BARBRY-GLAICHENHAUS]	A+	A+	Non noté	A+	A+
DEVELOPMENT OF INNOVATIVE THERAPEUTICAL STRAEGIES FOR DEPRESSION AND STROKE TREATMENT [BARBRY-HEURTEAUX]	A	A+	Non noté	A	A
THE POLYCYSTIN COMPLEX [BARBRY-HONORE]	A+	A+	Non noté	A+	A+
MECHANISMS OF GENE REGULATION IN PHYSIOPATHLOGY [BARBRY-LALLI]	A	A+	Non noté	B	A
MOLECULAR PHYSIOPATHOLOGY OF PHOSPHOLIPASES A2 AND THEIR MEDIATORS [BARBRY-LAMBEAU]	A	A	Non noté	A	A
MOLECULAR PHYSIOLOGY AND PHYSIOPATHOLOGY OF ION CHANNELS [BARBRY-LESAGE]	A+	A+	Non noté	A+	A+
ION CHANNELS AND PAIN [BARBRY-LINGUEGLIA]	A	A	Non noté	A	A
MOLECULAR AND CELLULAR PATHOPHYSIOLOGY OF VOLTAGE-GATED NA CHANNELS AND NEURONAL EXCITABILITY [BARBRY-MANTEGAZZA]	Non noté	A+	Non noté	A	A
MOLECULAR MECHANISMSOF NEURONAL PLASTICITY IN HEALTH AND DISEASE [BARBRY-MARIE]	Non noté	A+	Non noté	A	A
ACTIVITY DEPENDENT DYNAMICS AND ROLES OF SYNAPTIC SUMOYLATION [BARBRY-MARTIN]	Non noté	A+	Non noté	A+	A+
CELLULAR BIOLOGY OF NEUROPEPTIDES AND ASSOCIATED PATHOLOGIES [BARBRY-MAZELLA]	A	B	Non noté	A	A
GENOMICS AND EVOLUTION IN NEURO-ENDOCRINOLOGY [BARBRY-NAHON]	A	A	Non noté	A	A

C1 Qualité scientifique et production

C2 Rayonnement et attractivité, intégration dans l'environnement

C3 Gouvernance et vie du laboratoire

C4 Stratégie et projet scientifique

Statistiques de notes globales par domaines scientifiques

(État au 06/05/2011)

Sciences du Vivant et Environnement

Note globale	SVE1_LS1_LS2	SVE1_LS3	SVE1_LS4	SVE1_LS5	SVE1_LS6	SVE1_LS7	SVE2 _LS3 *	SVE2_LS8 *	SVE2_LS9 *	Total
A+	7	3	1	4	7	6		2		30
A	27	1	13	20	21	26	2	12	23	145
B	6	1	6	2	8	23	3	3	6	58
C	1					4				5
Non noté	1									1
Total	**42**	**5**	**20**	**26**	**36**	**59**	**5**	**17**	**29**	**239**
A+	16,7%	60,0%	5,0%	15,4%	19,4%	10,2%		11,8%		12,6%
A	64,3%	20,0%	65,0%	76,9%	58,3%	44,1%	40,0%	70,6%	79,3%	60,7%
B	14,3%	20,0%	30,0%	7,7%	22,2%	39,0%	60,0%	17,6%	20,7%	24,3%
C	2,4%					6,8%				2,1%
Non noté	2,4%									0,4%
Total	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

*** les résultats SVE2 ne sont pas définitifs au 06/05/2011.**

Intitulés des domaines scientifiques

Sciences du Vivant et Environnement

• SVE1 Biologie, santé
- **SVE1_LS1 Biologie moléculaire, Biologie structurale, Biochimie**
- **SVE1_LS2 Génétique, Génomique, Bioinformatique, Biologie des systèmes**
- **SVE1_LS3 Biologie cellulaire, Biologie du développement animal**
- **SVE1_LS4 Physiologie, Physiopathologie, Endocrinologie**
- **SVE1_LS5 Neurosciences**
- **SVE1_LS6 Immunologie, Infectiologie**
- **SVE1_LS7 Recherche clinique, Santé publique**

• SVE2 Ecologie, environnement
- **SVE2_LS8 Evolution, Ecologie, Biologie de l'environnement**
- **SVE2_LS9 Sciences et technologies du vivant, Biotechnologie**
- **SVE2_LS3 Biologie cellulaire, Biologie du développement végétal**

Présidence et
Services Centraux

Université
Nice
Sophia Antipolis

Nice, le 05 avril 2011

Affaire suivie par :
Eric DJAMAKORZIAN

Tél. : 04 92 07 69.05
Fax : 04 92 07 66 00

N/REF : 2011-1726

AERES
M. Pierre GLORIEUX
Directeur de la section des Unités
de recherche
20 rue Vivienne
75002 – PARIS

Ref : Rapport d'évaluation S2UR120001729 - Institut de Pharmacologie Moléculaire et Cellulaire (IPMC) - 0060931E

Monsieur le Directeur,

Faisant suite au travail effectué par le comité de visite de l'AERES et du rapport d'évaluation émis sur l'Unité de Recherche « Institut de Pharmacologie Moléculaire et Cellulaire » portée par l'Université Nice Sophia Antipolis, vous voudrez bien trouver ci-joint la réponse que nous désirons apporter à ce rapport.
Celle-ci réunie à la fois des corrections factuelles mineures et des observations de portée générale visant à apporter des précisions nécessaires au vue des remarques faites dans le rapport d'évaluation de l'IPMC.

Avec nos remerciements pour la pertinence et le caractère constructif des appréciations portées par le comité de visite,

Je vous prie de croire, Monsieur le Directeur, en l'expression de mes sentiments distingués

Le Président de l'Université
de Nice-Sophia Antipolis

Alb[illegible] MAROUANI

UNIVERSITE 1.1.1996

GRAND CHÂTEAU
28 AV. VALROSE • BP 2135
06103 NICE CEDEX 2

INSTITUT DE PHARMACOLOGIE MOLÉCULAIRE ET CELLULAIRE

Pascal BARBRY, Directeur

Sophia Antipolis, le 4 avril 2011

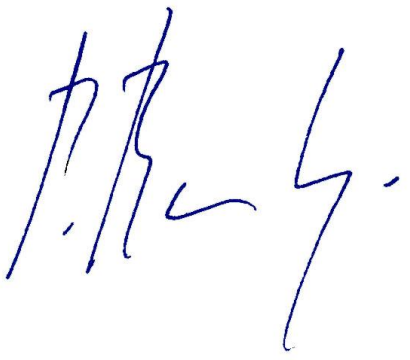
Monsieur le Président de l'Université de Nice Sophia Antipolis,
Monsieur le Président du CNRS,

Nous avons reçu le rapport d'évaluation de notre unité, l'Institut de Pharmacologie Moléculaire et Cellulaire, unité mixte de recherche UMR6097 du CNRS et de l'Université de Nice Sophia Antipolis.

Nous tenons à remercier le comité pour son travail, et pour ses avis précieux sur notre Institut et sur l'ensemble des équipes qui le composent.

Je vous prie de bien vouloir trouver ci-après, comme demandé, une lettre en anglais répondant à certaines remarques du rapport. Notre document est structuré en deux parties distinctes : la première (pages 2-9) contient des remarques générales à propos de l'unité et de certaines équipes. Estimant que plusieurs phrases du rapport doivent être modifiées car elles reposent sur des données factuelles erronées, une seconde partie (pages 10-24) contient l'ensemble des remarques pour lesquelles nous demandons une correction.

Je vous prie d'agréer, Messieurs les Présidents, l'expression de mes salutations distinguées.



Dr Pascal Barbry

General comments

We are grateful to the AERES Committee for its interesting comments and thoughtful recommendations. We are happy that the Committee has considered the IPMC as "an international class multidisciplinary research center". At the same time, we were surprised by the fact that IPMC was granted only "a good scientific production". We think that the more than 400 publications in international peer-reviewed journals (including 1 New England Journal of Medicine, 4 Nature, 4 Cell, 1 Annual Review of Biochemistry, 3 Science, 2 Nature Cell Biology, 2 Nature Medicine, 4 Journal of Clinical Investigation, 4 Journal of Experimental Medicine, 1 Immunity, 3 Nature Neuroscience, 2 Neuron, 4 PLoS Biology) with an average IF of 7.1 is more related to excellent than just good scientific production.

The Committee noticed the strong emphasis given to neurosciences during the last years, but did not acknowledge the other strong projects in relation with cancer, pulmonary disorders, inflammation, or epithelial cells. Since its creation in 1989, the research activity of IPMC has always been diverse and has led to the flowering of several flagship projects in different domains, in perfect accordance with its mission as an "Institute of Molecular and Cellular Pharmacology". The recent opening of a new building dedicated to neurosciences did not stop or dampen the development of competitive research in other fields. The presence of several successful projects on different biological topics is a feature of IPMC: it is indeed typical of an Institute of Pharmacology and thus it cannot be considered as evidence of a lack of scientific focus. However, and as mentioned below, we agree with the committee that future major axes of the Institute need to be better identified.

Neurosciences will definitely represent a major axis for development, backed up by the opening of the new building and recruitment of several new teams. **However, this development will not be exclusive, and we will pursue on our already existing flagship projects.** We agree with the committee that inflammation (which can also be related with work on neurodegenerative diseases) and epithelial biology are well positioned to become in the future major strengths of the Institute, which certainly needs to be better identified in our general scientific Project.

A better interaction between the different teams at IPMC will certainly contribute to further development of more global ambitious projects. Efforts in this direction have already been undertaken as illustrated by the recent fruitful collaboration of four different IPMC teams (teams E08, E13, E16 and E17), which led to an important publication in PLoS Biology in 2010 (spadin project).

The Committee also highlights that the strength of IPMC resides in the quality of its scientific staff, its state-of-the-art technological facilities, and its capacity to develop international class research in topics of medical relevance. This is well illustrated by the identification of two IBISA platforms, and by the participation of the functional genomics platform to the national infrastructure "France Génomique", which has been selected in the context of the "Grand Loan".

International visibility of IPMC, although already good, could be improved as pointed out by the Committee. Developing specific actions will be a priority in the coming months/years. Interestingly, several proposals of the Committee, such as the development of international exchange of students, were already planned by IPMC (see oral presentation of the SABLE project and annex 4 of the written project).

Mentoring for students and young group leaders, and better attraction of foreign students, post-docs and investigators, are also important proposals of the Committee, and we will develop actions in these directions to further improve our international visibility and attractiveness.

Regarding the governance, we appreciate the Committee's recommendations, even if we feel that the comments are a little severe. Over the last years, a huge work has been done to improve our organization and adapt it to the growing size of the laboratory (more space, more groups and more people). Many remarks of the Committee actually fit very well with the recent evolutions of our internal rules, which are all written (annex 2 of the output). Nine different workgroups currently have been introduced to the Committee (Executive committee, Group Leaders Council, Laboratory Council, Current affairs, Technical

Committee for Equipment…), and many important decisions have been triggered by these workgroups. However, the CNRS policy clearly states that the Director is the only person who is taking the final decision, following of course consultation of all *ad hoc* committees. It is also important to remind that the Director nomination has been backed up by the unanimous vote of the group leaders (29th of January, 2010) and 11 votes out of 17 (3 "con" and 3 "Null") of the Laboratory Council, suggesting that the quality of the decision making process and the transparency of the governance, although being certainly perfectible and prone to improvement, was not considered as a critical issue by the laboratory members, as it could be suggested from reading of the report.

Finally, we acknowledge that the technical support of some of the teams needs to be improved while maintaining the efficiency of our platforms. We will work on this point together with the University, CNRS and INSERM.

General comments on the "appreciation team by team" are given below. A more detailed rebuttal of the report is annexed at the end of the present document.

We would like to thank again the Committee for its work and recommendations that will be very helpful for the future of IPMC.

Comments on the specific appreciation team by team

Team E2 Physiological Genomics of Eukaryotes (Pascal BARBRY)

• *Results :* The Team is associated to more than 50 publications since 2006, which have been cited more than 600 times. First, second or senior positions represent more than 15 papers (>260 citations), including four papers with an IF over 10 (Nature Cell Biology, in press; Hepatology, 2008; Science, 2007; AJRCCM, 2007).

• *Impact:* The technological developments made by the Team have been instrumental for the setting of state-of-the-art functional genomics, attested by high impact publications, including recently accepted papers in Nature Genetics and Cell Research. Since 2006, the sole miRNA project has led to 10 papers, 2 patents and is associated with the organization of an international conference. This clearly underlines the recognition of the Team in this competitive field. Finally, the PI is also the coordinator of the InDiGen project (associating 7 HTS IBISA platforms) that has been selected in one call of the French Grand Loan ("France-Génomique" project).

• *Project:* We strongly disagree with the statement "This Team has some experience and skills in the field and should have more ambitious objectives to become internationally competitive". We are using state of the art approaches such as high throughput sequencing and functional studies with sophisticated model systems (e.g. air liquid primary epithelial cultures) to clarify the functional role of microRNAs. A key project targets the role of microRNAs in multiciliogenesis. The fact that our first paper on this topic was just accepted for publication in Nature Cell Biology (Marcet et al.) shows, in our opinion, that we are internationally competitive. This clearly establishes the Team expertise in that field and opens important new avenues regarding the role and mode of action of small regulatory RNAs in epithelial cell regeneration and differentiation in a physiological context, and their involvement in human pathologies.

Team E4 Role and regulation of natural killer cells (Véronique BRAUD)

page 17, conclusion on the strength: "post-doctoral fellow with good chances to be recruited at CNRS".

We would like to inform that the post-doctoral fellow is admissible at the INSERM CR2 concours (4th, with 6 positions available in 2011).

Team E5 Physio-pathology of prion diseases (Joëlle CHABRY)

The leader of the team E5 would like to comment on the committee report.

Regarding the productivity of the team, we published 7 peer-reviewed papers (J.Neurosci., Eur.J.Immunol., J.Virol., J.Neurochem, ...), 6 of them correspond to work entirely performed by our team,

as shown by the first and last authorships. We would like to highlight that, over the last four years, the team leader was also an invited speaker to 7 international conferences, including the **prestigious Gordon Conferences** on "Cannabinoids functions in the CNS" demonstrating the strong interest of the scientific community to our recent findings. Thus, we respectfully believe that our team displays a good productivity and international visibility.

The track record of fund raising was judged as "disappointing" by the committee. We would like to point out here that the team has been continuously funded by private and governmental grants among which the **highly competitive ANR "Neuroscience" (2006-2009)**. The team leader has also proved her capacity to raise important funds (ACI "Young Investigators", GIS, ANR…) over the last ten years. In addition, the team is well connected to the international community as proved by long-term and productive collaborations (J.Neurosci, BBA) with Drs. Priola (NIH, USA) and Dr. Heegaard (National Veterinary Institute, Denmark). More recently, new fruitful collaborations have been established with research groups headed by Drs. Di Marzo (Naples, Italy) and Béringue (INRA, France) as attested by 2 articles with co-authorship (Neurosci. and submitted manuscript).

There are also many evidence of the perfect integration of the group within the Institute with the existence of strong and fruitful internal collaborations. As explained during the interview, our studies on the roles of immune cells in prion infection have been greatly facilitated by advice, expertise and supplying of specific tools and transgenic mice held by the immunologists of IPMC (Teams E4 and E19). Moreover, we recently submitted a manuscript with co-authorship with team E17. Finally, as mentioned in the application file and during the interview, a strong collaborative work has been initiated with Team E15. Significant and promising results have already been obtained and a grant application was jointly filed by our teams (ANR- 2011).

Finally, we appreciate and agree with the recommendations of the committee to focus on the key role of PrP in the glutamatergic system regulation. Indeed, we clearly mentioned this strategy both in the application files and during the interview. Based on our most recent exciting and original results on the role of PrP in ethanol-induced neuronal excitability modulation, we shall submit soon a grant application (ANR "Mental health & Addiction") to carry on this aspect and explore the possible involvement of PrP expression on alcoholic behaviors and dependence. This will be done in collaboration with an expert electrophysiologist, Dr. Chavis (INMED, Marseille). Moreover, because we are aware of difficulties to raise funds on prion diseases, we have also developed a research path on Parkinson's disease. Based on our expertise and previously published studies (J. Neurochem, PlosOne), grant applications have been submitted to the ANR "Young investigators" and to the "France Parkinson" foundation by Dr. A. Petit-Paitel, the junior researcher of the team. In summary, significant efforts have been made to raise funds to achieve our exciting projects.

<u>Team E10</u> Mechanisms of gene regulation in physiopathology (Enzo LALLI)

I would like to thank the AERES evaluation committee for its report on the activity and projects of my research team. However, I would like to express here my disagreement with some of the major conclusions reached in the report:

1) I strongly believe that the results produced by our team during the past four years are situated at the top level in the field of adrenocortical physiopathology, as shown by the high citation rate of several of our publications and by our international (as shown by the number of invited conferences, awards received and invited review papers published) and institutional (as shown by the recruitment of tenured scientists) recognition.

2) Similarly, I strongly disagree with the quite negative evaluation of our research projects made in the report. Our projects are the logical continuation of our previous cutting-edge research, as shown by their approval and funding by some of the most important national and international funding agencies (ANR, INCa, FP7, NIH). In particular, the translational part of our projects is fully justified by the relevance of the

results obtained in the field by our team and by the urgent need of novel, more active drugs to fight against adrenocortical cancer.
Conversely, I very much appreciate the constructive comments of the committee about focusing of the activity of our research team. I see Dr. Demolombe's contribution as a strength to extend our competence in a different field of the broad domain of gene regulation and not as a weakness. We have decided to join our forces and to take the risk of pursuing new, innovative projects. However, I agree with the committee about the need to keep the research pursued by Dr. Demolombe as focused as possible and so discussions about the continuation of her activity in our team are in process and a decision will be taken within six months from now.

Team E11 Molecular physiopathology of phospholipases A2 and their mediators (Gérard LAMBEAU)
We would like to thank the committee for their very positive appreciation of the team, especially for pointing out its strength and originality, and facts such as « the quality and impact of the research results is very high and acknowledged by a large number of publications in good to high impact factor journals, invited conferences and patents », as well as « the team has established a very good network of local, national and international collaborators… » and « funding from multiple sources has been obtained ». Two publications are now Top 1% articles (Lambeau and Gelb (2008) Annu. Rev. Biochem. 77, 495-520; Beck et al. (2009), N. Engl. J. Med. 361, 11-21).
We also thank the committee for their positive comments and recommendations in the conclusion section. We will of course take them into account.
1. Our aim is to develop internal expertise, especially for the subprojects dealing with the role of sPLA2 and PLA2R1 in cancer and membranous nephropathy.
2. Concerning the relatively small size of the team, we will quickly hire at least one post-doc (arrival planned for October 2011), a Master/PhD student, and possibly another tech ingenior funded on grants. We have had one senior assistant professor in the group from the University of Cergy-Pontoise, but we could not stabilize her position in the laboratory. Efforts will be made to hire another senior researcher whenever possible.
3. Concerning the exploration of the role of sPLA2s as biomarkers of disease and as novel biotherapeutic molecules, we have already obtained a grant to perform translational research from the call « ANR émergence », and we are now applying to the call « ANR RPIB (Recherche Partenariale et Innovation Biomédicale) » in collaboration with a start-up company. The 6 patents already issued plus an additional 2 patents which are pending will protect our intellectual property towards such goals.

Team E12 Molecular Physiology and Physiopathology of Ion Channels (Florian LESAGE)
We thank the committee for its positive appreciation of our results and projects and for its helpful recommendations. Several points that the committee may have misunderstood or overlooked are clarified hereafter.

- About governance/strategy of the team: several times, the report puts emphasis on the fact that the team comprises 3 inserm/cnrs researchers and that given this number, "*the senior members may be a bit overrepresented compared to junior members*" and "*the number of papers could be higher*". Both Guillaume Sandoz and Sylvain Feliciangeli came initially from outside for a post doc in the group. Then they got CR2 permanent positions in the same group, a CNRS position for G Sandoz in 2005 and an Inserm position for S Feliciangeli in 2007. They were promoted 4 years later as CR1. Talented but not yet senior scientists, they are on the tracks to seniority: They are developing original research programs, and in 2011 both researchers have applied to "young researchers" ANR grants. If they are funded, they will have

financial resources for hiring post docs from abroad. The objective for the next years is to favor the emergence of new scientific leaders.

- About scientific production: the team has produced 3 reviews and 8 original articles (1 Cell, 2 PNAS, 2 EMBO J, 2 J of Neuroscience, 1 JBC), 9 of them with at least one member of the team in a principal position. The committee seems to imply that it is a bit low for a team comprising 3 permanent researchers. But the committee may have noticed that one of them was on sabbatical from July 2009 to the next summer for acquiring new expertise. During this period, G Sandoz has published as first author one more article in PNAS and one in Nature Communications. This raises the production of the 3 researchers to 10 articles in excellent to top journals. Also, I spent a fair amount of time to CSS1 of Inserm as a nominated member, whereas G Sandoz and S Feliciangeli were spending time on teaching for total of 237 hours. Another point that the committee may have also noticed is that the team was directly responsible for the production of 6 original articles in major journals with only 323 k€ of grants which is a well above the average. These results were obtained using mainly a support from the Medical Research Foundation (FRM), the National Research Agency (ANR) not having supported this research despite repeated applications. Having proven that we were effective as an independent team, we hope that our current and future applications to ANR will be more successful, which will give us the possibility to recruit post docs to expand our research activities.

- About the impact of our work: Initially in the laboratory directed by Michel Lazdunski then in my own group, I have pioneered the development of a new research field. Background potassium channels are now extensively studied by different teams at IPMC but also by many groups in the world. More than 100 papers are published each year that are directly related to this family of ion channels. My work is highly cited: around 500 citations per year for the last 10 years, an average of 85 citations per article for a total of 7500 citations, h-index 44 (*ISI Web of Science, Reuters Thomson*). Nevertheless, the committee preferred to stress the fact that "*The number of citations the publications receive is relatively modest; for instance the Cell paper from 2007 yielded 19 citations thus far*". This article in Cell shows that data and conclusions of another paper published in the same journal and based on our initial work on background potassium channels are erroneous (Rajan et al, Cell 2005, 78 citations). But we next published a JBC paper with more positive results on the same topic, and in 2010 this article was in the Top 1% of the most cited articles in its category. The same year, two other articles were in the Top 1%: Gestreau et al, PNAS 2010 and Guyon et al, J Neurosci 2009. The other articles were for the majority of them in the Top 10%.

- About funding: the committee recommends "*More participation in European networks to apply for european funding*" and that "*All Inserm/cnrs researchers should spend a significant amount of time on acquiring funding*". In 2007, I have contributed as "ion channel" work package leader to the writing and submission of a proposal (EUROPUMP) to FP7 programme. But it has not been granted. We will try again. At the National level we have submitted this year 4 applications to ANR and one to FRM. As stressed during my oral presentation, all the team members have contributed to the writing of these proposals.

- About our research projects: globally they were positively evaluated by the committee. But "*The rationale and the feasibility of the project on acquired channelopathies are not entirely clear*". This project related to neurological disorders promoted by postinfectious or paraneoplastic autoimmunity against ion channels has been selected in 2010 by a national committee including neurologists and neuroscientists (translational research award to FL), and is carried out in collaboration with clinicians of the Neurology Unit, Hospital Pasteur, Nice. For 2011, ARC (Cancer Research Foundation) granted a 12-month salary to Franck Chatelain. This project is clearly on the risky side but we believe in its potential for developing new diagnostic tools and therapeutic opportunities. Another recommendation from the committee was that " *the*

team may wish to explore potential local collaborations for KO mice phenotyping". We are already engaged in such a local collaborative effort. On this topic, we have already published with teams 10 and 17, and with the team of Jacques Barhanin that has moved to Nice. Some of our mice have also been studied by teams 5 and 8, or are still under study in teams 9 and 13. We also provided antibodies and plasmids to team 16. In summary, 7 teams out 19 of IPMC are or have been associated with the study of background potassium channels and related KO mice.

Team E13 Ion Channels and Pain (Eric LINGUEGLIA)

The Committee has some concern about the leadership of the team leader because some publications are still co-signed by Michel Lazdunski, the former lab director. We can reassure the Committee by indicating that Michel Lazdunski is not involved at all in the management and decision process of the team. His authorship in some of our articles (our choice) was justified by either i) his contribution in some initial aspects of the work (the team was created in 2007), ii) his significant contribution in critically revising some of our manuscripts in the very last stages of preparation. The contribution of Michel Lazdunski is clearly a plus for the team, and is further supported by its position as senior vice president and chief scientific officer of the spin-off company Theralpha, with which the Committee recommends to strengthen the partnership. This contribution remains however limited and does not in any way jeopardize the leadership of the group leader, who was promoted Research Director by Inserm in 2008 and has attained national and international recognition in his field as testified by several invited reviews published and 8 invitations to national (2) and international (6) meetings over the 4-year period.

We would like to point out that the appreciation of the attractiveness of the team was based on the IPMC written report, which was listing people present in the team by June 30, 2010 (with only one graduate student). As mentioned in the oral presentation, we have actually attracted during the last 4 years 5 Master students (M1 and M2) and one visiting scientist from the University of Barcelona (12 months), i.e, a number higher than the one mentioned in the AERES report. We nevertheless agree with the Committee that the number of Ph.D. students and post-docs needs to be improved.

The Committee questioned our ability to investigate the role of ASICs in synaptic transmission and plasticity in the spinal cord. We acknowledge that the techniques of electrophysiological recordings in vivo and in spinal cord slices are not yet present in our team, but we expect these techniques to be quickly available in the lab based on (i) our long-term expertise in electrophysiology (our team comprises four highly skilled electrophysiologists, including Jacques Noël who has performed hippocampal slice recordings in Graham Collingridge's lab in Bristol), (ii) our planned collaboration with the group of Massimo Mantegazza at IPMC (team E14), who has a strong expertise in electrophysiological recordings in slices, (iii) our good connections with groups of the French INSERM Research Network on Pain, which are recognized experts in electrophysiological recordings in the spinal cord (both in vivo and in slices, like in Bordeaux) and (iv) the availability at IPMC of two dedicated electrophysiology setups for slice recordings and the availability in our group of an electrophysiology setup for in vivo extracellular recordings. As highlighted by the Committee, we have already demonstrated our ability to develop high-skill electrophysiological techniques such as nerve-skin preparation unique in France and recently established in the lab.

Team E17 Genomics and Evolution in Neuro-Endocrinology (GENE) (Jean-Louis NAHON)

We thank the committee's members for their positive comments regarding the "*past record of excellent and original contribution*" and the fact that the team (has) " *the know-how on the proposed projects, which are also original*".

Regarding the criticisms concerning the project that appears "*too diverse, unfocused and ambitious*" we would like to stress the following points: 1) too much diversity has been recognized as an overt weakness item in the SWAP analysis presented by our team during the examination with the committee. It resulted mainly from the need, during the past four years, to "open" our conceptual and technical thought frames in order to address general issues such as "where, when and how primate-specific genes regulate brain functions" (a rather ambitious question raised in the APES project supported by EU) and "what is the relative role played by neuropeptides/cytokines/chemokines in the central control of feeding behavior and energy homeostasis" (a "hot topic" in the field of neuroendocrinology). Incidentally, these two seminal questions have been voluntary emphasized within our team title "Genomics and Evolution in Neuro-Endocrinology". 2) We have identified four specific sub-projects that tend to integrate these two fields. We agree that the time schedule of these sub-projects was not explicit. However, two out of the four sub-projects, the characterization of the PMCHL/MCH gene expression-functions in cellular models and in primate brains under normal and pathological conditions are largely under way and should be completed within the next two years. The most promising and cutting-edge projects have already been initiated (including the "*exciting*" "trans-splicing" project as noted by the committee) and we have established strict priorities based on our most recent achievements.

A corollary of this "diversity" is the acknowledged paucity in the publication level but certainly not in the number of publication per full-time researchers that is not "less than a publication per researcher per year" but in between two to three per year (precisely 2,58/year). The discrepancy between the committee and our own calculations resulted likely from the underestimation of the articles signed by several members of the team that rather testified of good interactions and focusing of the projects. By the time the committee left the IPMC, four additional articles were published or submitted for reviewing (see list below). On the other hand, we agree that our most recent articles were not published in high IF journals (albeit J. Neuroscience is usually considered as a top journal in the field) but they were highly cited (for instance Guyon and Nahon, 2007, J Mol Endo was already cited 44 times; source ISI Web of knowledge) and contributed to the establishment of new concepts such as the role of chemokines in neurotransmission that is now fully recognized and the clustering of "primate-specific" genes within "gene nurseries". In addition the output of our works was also recognized by the scientific community based on the numbers of invited papers at international meetings (more than two per year for two senior authors).

A particularity of our team is the technical skills and expertise in electrophysiology on brain slices recently brought by the recruitment of Alice Guyon as a permanent CNRS investigator. This expertise was and is being shared frequently through collaborations within the IPMC (teams of J. Chabry , C. Heurteaux, F. Lesage and J. Mazella) and other teams in France and Europe (team of P. Kitabgi/S. Melik-Parsadaniantz/W. Rostène, Hôpital Saint-Antoine, Paris; team of R. Stumm, Magdeburg, Germany). This strong expertise has generated several major contributions (see for instance Kolodziej A et al J. Neuroscience 2008; Mazella et al, PLoS Biology 2010). Such highly structuring interactions within IPMC teams were surprisingly not highlighted in the committee report with criticisms pointing out the lack of collaborations among the IPMC teams.

Criticisms regarding the "*recruitment (that) seems to be low, may be due to limited funding…*" and the fact that " *two of the three big grants have been obtained in collaboration. It is not clear that they reflect the ability of the PI to raise money*" are, at best, reflecting misunderstanding of the submitted documents or, more unexpected, lack of knowledge regarding the mechanisms of the granting process in France and Europe that, until very recently, were based on collaborative projects. During the last four years I, and I use this pronoun on purpose, raised roughly **1 113 000 €** from EU grant (WP2 I led alone…and in many times I took the leadership in driving the APES contract as the CNRS DR20 staff could confirm it), ANR-MNP grant (I am the "Coordinator" and collaborate with the team of E. Bezard who is partner 2), CNRS-Hôpital Laval (Québec) (PI of a project made in collaboration with D. Richard), CNRS-INSB "Biothèque Primate" (PI of the project at the IPMC). I also obtained supports from the French Medical

Research Foundation/FRM (as member of the Scientific Council) and France Parkinson Association (only 100 K€ in total). In addition I strongly urged other senior members of the team to participate to the exalting funding race and Alice Guyon (CR1 CNRS) also succeeded in obtaining financial supports from the "Fondation de France" and CNRS-INSB (a highly competitive PEPS contract), and Gregory Conductier (Post-doctorant) has recently received the french "Société de Nutrition" Award with joined financial support. With this funding, **I have recruited 6 engineers and 3 post-doctoral fellows** for time periods in between 2 to 4 years as well as 10 graduate students (the information was indicated in the § Main Achievements). The ability to raise more than 1 million euros within 4 years and to recruit for the necessary projects up to 11 engineers/researchers (including two PhD students on MESNR funding) positioned our team in the top level of the funding "collectors" and non-permanent fellow "recruiters" at the IPMC.

Overall I thank the Committee's members for their constructive remarks regarding refocusing of our projects and greatly appreciate their support in the need to obtain a technician position. Finally, I hope that I convinced the Committee about my capacity to raise funds and to ensure long-term viability of the team.

List of recently published or submitted articles from team E17:

- Conductier G., Blondeau N., Guyon A., Nahon J.L. and Rovère C. The role of monocyte chemoattractant protein MCP1/CCL2 in neuroinflammatory diseases (2010) J. Neuroimmunol. 224, 93-100
- Rostène W., Guyon A., Kular L., Godefroy D., Barbieri F., Bajetto A., Banisadr G., Callewaere C., Conductier G., Rovère C., Mélik-Parsadaniantz S. and Florio T. Chemokines and chemokine receptors: New actors in neuroendocrine regulations. Front. Neuroendocrinol. (2011) 32, 10-24
- Conductier G., Nahon J.L.** and Guyon A.** Dopamine depresses melanin concentrating hormone neuronal activity through multiple effects on a2-noradrenergic, D1 and D2-like dopaminergic receptors (2011) Neuroscience 178, 89-100
- Dalmas E., Rouault C., Abdennour M., Rovère C., Rizkalla S., Bar-Hen A., Nahon J.L., Bouillot J.L., Guerre-Millo M., Clément K. and Poitou C.Variations in circulating inflammatory factors are related to changes in caloric and carbohydrates intake early in the course of surgery-induced weight reduction-Submitted to Am.J.Clin.Nut.

Point-by-point answers to the report from the AERES review committee

We would like to correct here factual errors made by the committee on the report and we would really appreciate these corrections to be made before publication of the final report.

Point-by-point answers to the report from the AERES review committee on the overall appreciation of the research unit

Page 3
- **Introduction**
  - **History and geographical localization of the research unit, and brief presentation of its field and scientific activities**

"among which 74 researchers and 51 technical personel with tenured positions"

These numbers correspond to projections for 2012. We are **"66 researchers and 39 technician/engineer/administrative staff with tenured positions"**

Page 3
- **Introduction**
  - **Management team**

"an executive commitee composed of the director and leaders of teams 1 and 6"

This is the current, but in no case a marmoreal situation! As written in the Internal Rules **our executive committee is composed of the director and at least two team leaders**:
« Le comité de direction a pour mission d'assister le directeur pour les décisions à prendre concernant notamment les orientations scientifiques, les demandes et répartitions de moyens (budgétaires, humains, équipements, locaux) et l'organisation de l'Institut. Le directeur arrête la constitution du comité de direction, qu'il présente au CdL. Il est constitué du directeur, du directeur adjoint s'il existe, et de 2 ou 3 chefs d'équipe, ou sinon des chefs de départements s'ils existent ; ces représentants ne peuvent pas siéger au CdL. Il se réunit au moins une fois par mois, et peut comporter des invités, selon les thèmes traités. Un relevé de décisions est diffusé aux chefs d'équipes. »

Page 4
- **Table**
  - Future N5 and N6 = "?"

AERES does not ask to mention these numbers: **the question marks should be removed**.

Page 5
- **Overall appreciation on the research unit**
  - **Summary**

"Initially largely focused on ion channels pharmacology and pathophysiology under the directorship of Michel Lazdunski, it has broadened its scope to encompass many aspects of functional genomics, with a net diversification, in particular towards neuroscience. The major re-organizational work, which has been carried out during the last years, has originated in large part through the recruitment of four external new groups (including 3 ATIP laureates), the splitting of the former Lazdunski team in 3 new teams and the recent addition of an INSERM team"

The original institute was not uniquely focused on ion channels, as illustrated by the thematics of the founding groups: M. Lazdunski, "Ion channels and ion channel physiopathology"; M.Chabre (and P. Chardin), "Small G proteins, structure-function, implications in cancer"; J.P. Vincent, "Neuropeptides

and neuropeptidases"; C. Frelin. "Endothelial cells (endothelin and Na+/H+ exchange system)"; J.L. Nahon, "Neuroendocrinology"; N. Glaichenhaus, "Immunology, immunopathology". Since these early years, it is obvious that the high dedication of talented IPMC scientists has ensured the development of several flagship projects in different areas. The addition of an INSERM team is not a recent event, since the Glaichenhaus Team was one of the founding Team of the IPMC. Finally, the re-organizational work carried out during the last years does not originate *"through the recruitment of four external new groups, etc…"*, but rather from the opening of a new building entirely devoted to "Neuro-Molecular Medicine". The recruitments are rather consequences of this opening.

For us, **IPMC was already multi-thematic under the directorship of Michel Lazdunski, and as such it has developed over the years a large expertise and recognition in different fields, including in neurosciences. The major re-organizational work, which has been carried out during the last years, has originated in large part through the opening of a new building devoted to "Neuro-Molecular Medicine", allowing the recruitment of four external new groups (including 4 ATIP laureates) and the reorganization of the former Lazdunski, Vincent and Chardin teams in 8 new teams.**

NB: there were 4 ATIP, since Barbara Bardoni arrived from Nice with an ATIP+.

Page 5

- **Overall appreciation on the research unit**
  - **Weaknesses and threats**

"Lack of scientific focus: though the overall research activity of the institute is oriented mostly towards neurosciences, developed projects and biological issues are extremely diverse and include cancer, pulmonary disorders, inflammation, epithelium cells…"

One can only disagree with this point. "IPMC" stands for "Institute of Molecular and Cellular Pharmacology"!... As mentioned above, the research activity was diverse since the origin, and lead to the flowering of several flagships projects in link with cellular signaling, cardiovascular system, cancer, inflammation or epithelial cells, and some of them were commended by the Committee. Emphasis that the Committee is giving to Neurosciences is certainly justified by the opening of a new building, and indeed, the initial plan for it was to create a distinct "Institute of Molecular Neuromedicine". This project did not come to reality, due to some problems at the University, leading to a merge with IPMC against the will of the founder and after his retirement from the direction. Two distinct Institutes with a coordinated structure would have perhaps provided much more visibility for the Committee. In any case, considering the presence in the building of several successful topics as a demonstration of a lack of scientific focus appears totally misleading. This sentence is also in contradiction with the last "strengths and opportunities" that says: *"More generally, the diversity of the expertise of the teams open the way for ambitious transversal projects"*. **This sentence should be removed or rephrased.**

Page 5

- **Overall appreciation on the research unit**
  - **Weaknesses and threats**

"As a consequence, there is a feeling of a lack of strategic vision for the institute's general ambition and scientific objectives that would render the IPMC more visible at the international level"

As explained to the Committee (Annex 4, page 3 of the project and oral presentation), IPMC has developed a recognized expertise on a wide variety of biological molecules. All these molecules, often identified for the first time at IPMC, are directly involved in, and constitute new therapeutic targets for,

neurological disorders, including Parkinson's and Alzheimer's diseases, stroke, depression and pain, as well as cancer, obesity, inflammatory, respiratory and cardiovascular diseases. By determining the normal and pathological functions of these molecules, IPMC investigators are contributing directly to the development and evaluation of new treatments against several devastating diseases. Their work is in direct line with several unanswered questions at the forefront of science for the next century (as detailed at: http://www.sciencemag.org/cgi/content/full/309/5731/78b), which elucidations represent some long-term scientific goals for the biological community: To what extent can we stave off neurodegenerative diseases? How therapies, especially in neurological and cardiovascular contexts, can be made more effective? What keeps intracellular traffic running smoothly? Can we predict how biomolecules will fold, and how they find their partners? What are the roles played by RNA in genome function?
We fully understand the danger of a thematic dispersion, but we also believe that our past successes are giving some credence to our current strategy.
In the difficult financial context crossed during these latest years, IPMC has been able to structure successfully several world-class scientific projects, while modernizing its equipments, and installing new scientists. We defined as a prerequisite for any future success an upgrade of the general infrastructure, after more than 20 years of intensive use. This point was commended by the committee. This explains our efforts regarding the general equipments of our laboratory, including animal care, imaging and functional genomics (NB: there is currently no bioinformatics facility). This probably explains why the Committee may have considered that the choices made by the unit were more driven by the technology than by the science. This does not take into account the long-term existence of different excellent projects, outside neurosciences, which don't correspond to some recent and unjustified diversifications, but rather follow a past successful history. This multi-thematic strategy is also well adapted to the real dimension of our University, and provides to ambitious and talented scientists an adapted environment for their development. We fully agree that further efforts will still be mandatory for rendering IPMC even more visible at the international level, but we do insist on the fact that this development will follow the multi-thematic strategy that we have developed for more than 20 years, and which has already produced so many successes. As said, we understand the importance to develop our visibility and this will be one focus of the next contract. **This sentence should thus be rephrased.**

Page 6
- **Overall appreciation on the research unit**
  - **Weaknesses and threats**

"For some groups: one might wonder if the environment of the institute is adapted"

This sentence is vague, and does not allow any specific answer. It should be removed.

Page 6
- **Overall appreciation on the research unit**
  - **Weaknesses and threats**

"The Committee could note a lack of transparency of the general governance and low general involvement of the group leaders in the institute's decision making process"

Page 6
- **Overall appreciation on the research unit**
  - **Recommendations to the head of the research unit**

"- Rethink the decision making process and improve the transparency of the governance"
"- Actively involve all group leaders in the decision making process, in particular regarding allocation of resources (mainly space and technical personnel)"

Page 9

- **Specific comments on the research unit**
  - **Appreciation on the strategy, management and life of the research unit**

"More generally, regarding the governance of the unit, the general impression was that there is a lack of transparency and that the mechanisms for allocation of resources in opaque. The committee could not understand the mechanisms for allocation of space or of technical personnel to teams. Similarly, the rules for career promotions, bonus allocation or mobility of ITAs are unclear. This lack of transparent governance was repeatedly expressed during face to face meetings with team leaders, with ITAs and researchers"

Page 9

- **Specific comments on the research unit**
  - **Appreciation on the strategy, management and life of the research unit**

"The evaluation committee strongly felt that efforts should be made to improve the general governance by i) improving the communication between the governing bodies and the personnel and explaining better the rules and rationale for resource allocation, ii) implicating more the different group leaders in the decision process at the institute level, maybe by increasing the size of the executive committee, or by giving a more important decisional role to the team leader committee, iii) improving the career development follow-up for all categories of personnel, including ITAs, students, post-docs and researchers, maybe by creating a dedicated career development committee."

Page 9

- **Specific comments on the research unit**
  - **Appreciation on the project**

"Allocation of ressources, in addition to being somewhat unclear, was not enough concentrated on big projects"

We are open to constructive ideas. Over the last years, a huge work has been done to improve our organization and adapt our governance to the larger size of the laboratory (more space, more groups and more people). Many remarks of the committee fit with recent evolutions of our internal rules. The fact that these rules are so far only written in French, while illustrating our need to reinforce our internationalization, can hardly be taken as a demonstration of any kind of opacity. Nine different workgroups currently exist (Executive committee, Group Leaders Council, Laboratory Council, Current affairs, Technical Committee for Equipment…). Any goodwill can participate, and many important decisions have been triggered by these workgroups. However, it is also important to stress that according to the CNRS policy, the Director is the only person who can be legally engaged by the collective decisions. For this reason and also to avoid potential conflicts of interest, the final decision by the director, following consultation of *ad hoc* committees, often represents the wisest option. The unanimous vote of all the group leaders (29th of January, 2010), which was followed by a large election by the Laboratory Council (11 "pro", 3 "con", 3 "Null"), suggests that the quality of the decision making process was not considered as an issue by the laboratory before the visit of the Committee.

As explained orally to the committee, the allocation of space has so far followed past recommendations by our evaluation committees, as long as these latter provided clear advices. We will rapidly improve our rules, to define more clearly how are allocated the resources.

Page 6

- **Overall appreciation on the research unit**
  - **Recommendations to the head of the research unit**

"Recommend stronger support by the university for improving the conditions for the student (transport, food)"

The time needed to shuttle by bus from the laboratory to Nice, Antibes or Cannes is maximum 1 hour, and costs less than one euro!... Within 1 km, there is a University Restaurant open to all students and professors, a restaurant opened to persons paid by CNRS and Inserm, and we have two dining rooms. **This recommendation is quite obscure and should be removed!**

Page 7

- **Specific comments on the research unit**
  - **Appreciation on the results**

"23 Ph.Ds. have been defended during the past four years"

This is **26**

Page 8

- **Specific comments on the research unit**
  - **Appreciation on the impact, the attractiveness of the research unit and of the quality of its links with international, national and local partners**

"The IPMC has been successful in raising funds from various sources: ANR, European contracts, industrial contracts, foundations, charities, and local authorities CG 06, PACA Region... with 1.5-3M€ per year in external contracts. The amount of funding from external sources (24.8%) as compared to recurrent money from CNRS/INSERM/university is good but could be improved"

24.8% represents the fraction of funding from external sources relative to the consolidated budget (including labor costs of tenured staff). This value was provided for helping our foreign colleagues. If we then calculate this percentage outside institutional salaries, the 24.8% should be replaced by "above 70%, which means that external resources represent twice the amount of the core funding institutional budget. The ratio is in reality even higher, since a large part of the CNRS budget is in reality used for the infrastructure (~0.5M€ per year) (79% in that case). **This paragraph should be rephrased.**

Page 8

- **Specific comments on the research unit**
  - **Appreciation on the strategy, management and life of the research unit**

"The important dedication of human and financial resources to these core facilities is an excellent strategy that should in the long run foster the development of the institute and the recruitment of other team leaders, students and post-docs.
As a drawback, there is a general lack of technical support dedicated to individual teams, with many senior teams missing permanent staff technical personnel and having to rely on temporary recruitments. While it is laudable that the institute dedicates important resources to core-facilities, a more balanced distribution of technical personnel between facilities and teams should be envisioned."

The second paragraph contradicts the "excellent strategy" dedicating resources to foster the core facilities. In addition, a big institute cannot underestimate the need of personnel to run specific, strategic facilities: for example, 2 (1 tenured) persons for the washing and disinfection service, 6 (4 tenured) for animal care facility, 2 for cellular imaging, 7 (6 tenured) for functional genomics, proteomics and DNA sequencing. The opening of a new 3000 m² building did not lead so far to the net creation of personnel. This is the main explanation for the general lack of technical support to the teams, which is clearly a

result of the freeze of fresh recruitments by our supporting institutions since the last 3 years, while welcoming 4 new teams, and despite the successful recruitment of permanent scientists. In our opinion, the only solution is that our supporting institutions should increase the technical support to our institute. During the oral presentation, the situation of several planned retirements was also clearly stated, and we clearly warned the committee and our establishments about this situation. **We consider that the juxtaposition of these two paragraphs is an implicit support of our demands to our establishments, but we would have clearly preferred an explicit statement.**

Page 9

- **Specific comments on the research unit**
  - **Appreciation on the strategy, management and life of the research unit**

"There was a marked feeling for a difference in career development between ITAs working in teams and those working for core-facilities, the latter being favored. The absence of clear knowledge of the mechanism regarding the decisions relating to their careers was striking."

A survey over the last 10 years clearly shows that the rate of promotions for the ITA in teams is equivalent to the promotion for the ITA in facilities (7 and 5 for the teams and for the facilities, respectively, for 14 ITA in teams and 15 ITA in facilities). The rules for career promotions, bonus allocation or mobility of ITAs have been explained many times: the low rate of success at a national level sometimes give the impression to the agents that the direction is not supporting them, while the results of the IPMC during the last three years are excellent, thanks to an efficient coaching of the agents. **This paragraph should be rephrased.**

Page 9

- **Specific comments on the research unit**
  - **Appreciation on the project**

"On the whole, the institute hosts a series of good to excellent projects. However, as described above, the IPMC represented mainly a collection of individual projects, rather than an organized effort toward solving well identified major questions. The committee felt a need to decide on stronger international visibility as a whole.
Team 5 was felt in danger for the future due to absence of a mainstream project, low funding and lack of sufficient personnel in the project.
Team 10 failed to convince on the solidity of its strategy, both due to the absence on an ambitious project and the disconnection of the new projects from the main stream of the team.
Allocation of ressources, in addition to beeing somewhat unclear, was not enough concentrated on big projects.
The institute hosts several individual cutting edge projects, but several team projects could be more ambitious. There is a lack of institution level ambitious project"

Discussions have been carried out with Team 5 and Team 10, and plans of action have been defined for the next 6 months regarding their scientific projects. They are detailed below. Questioning the allocation of resources, not enough concentrated on big projects, is just nonsense, since the institutional budget of the unit is steadily decreasing, despite an increase of our perimeter. But we will naturally work to further develop our visibility. We insist on the fact that the development of ambitious projects at a laboratory level will be considered as long as it will maintain the outstanding publication records of the individual groups (see above). **This paragraph should be rephrased.**

Point-by-point comments to the team E2's report
(Physiological Genomics of the Eukaryotes)

Team leader : **Pascal Barbry**

Page 12

- **Appreciation on the results**

"The impact of the research is limited, with some flagships due to successful collaborations"

First, second or senior positions represent more than 15 papers (>260 citations) since 2006, including four papers with an IF over 10 (Nature Cell Biology, in press; Hepatology, 2008; Science, 2007; AJRCCM, 2007), and usually correspond to scientific projects with specific grants for the Team. During the same period, the Team is also associated to more than 50 publications, which have been cited more than 600 times. The impact of the Team is also important through its contribution for technological developments in high throughput sequencing that corresponds to a very time-consuming activity. This work has nevertheless been instrumental to set up a state-of-the-art functional genomics platform. The Team contribution is acknowledged by its association to high impact publications, including recently accepted papers in Nature Genetics and Cell Research. Since 2006, the miRNA research project, which has been initiated by the Team, has led to 10 papers and 2 patents. The Team has also organized an international conference (*"MicroRNA and small non coding RNA: new actors in physiopathology"*). All these elements clearly underline the recognition of the Team in this competitive field. Finally, the PI is also the coordinator of the InDiGen project (associating 7 HTS IBISA platforms) that has been selected within "France-Génomique" in the context of the recent calls of the French Grand Loan. **We therefore ask the removal of the sentence about the *"limited impact of the research".***

Page 13:	**Page 13:**
• **Appreciation on the project:**	• **Conclusion:** ○ **Weaknesses and threats**
"However, the presentation of the project lacks convincing thoughts about the overall vision, and hypothesis concerning the role of miRNA in biological processes"	*"The presentation of the project lacks convincing thoughts about the overall vision, and hypothesis concerning the role of miRNA in biological processes in vivo"*

An important part of our future project is indeed based on our own results showing the role of specific miRNAs during multiciliogenesis that has now just been accepted for publication in Nature Cell Biology (where B. Marcet appears as a first author, and P. Barbry as a senior author). This paper clearly establishes the Team expertise in the international competition. It also opens important new avenues regarding the role of small regulatory RNAs in the context of epithelial cell regeneration and differentiation, including their modes of action in a natural context, and their involvement in human epithelial pathologies. We regret that the Committee missed the importance of studying small regulatory RNAs in well characterized human primary cultures, rather than in cell lines, and also the potentials of inter species comparison in different *in vivo* and *in vitro* models such as those that we have developed for studying multiciliogenesis (Xenopus,…). From that perspective, the capacity to perform genome-wide studies including on animals for which sequence information is incomplete represents a major strength. **These two (and identical!) sentences should be modified.**

Page 13

- **Conclusion:**
  - **Recommendations**

"This team has some experience and skills in the field and should have more ambitious objectives to become internationally competitive. Keeping a focus on the physiopathology of epithelial structures will help acquiring visibility. In that respect the team should develop connections with other groups at IPMC working on epithelial cells"

We appreciate the wise recommendation made by the Committee, especially regarding the development of connections with groups at IPMC working on epithelial cells. We will simply add that two investigators of the Team have made in the past important contributions in the epithelial field by achieving the first expression cloning of the amiloride-sensitive epithelial Na^+ channel. They then established several important physiological and biochemical properties of this target of aldosterone (in kidney and colon) and glucocorticoids (in lung). The PI has also made some discoveries regarding CFTR, the cystic fibrosis gene product, showing for the first time the altered chloride-ion channel kinetics associated with the frequent ΔF508 mutation, or identifying the first direct opener of CFTR. Regarding present international competition, cf. our Nature Cell Biology paper (Marcet et al, in press).

Point-by-point comments to the team E3's report (Physiopathology of Mental Retardation) — Team leader : **Barbara Bardoni**

Page 15

- **Appreciation on the project**
  - *"Projects for the coming years consist of FP7 and e-rare funded projects"*

Indeed, our projects are funded by **Fondation pour la Recherche Médicale (Équipe FRM, AO-2009 300K€),** ANR E-rare (200K€) and FP7 (45K€).

team E05's report (Physio-pathology of prion diseases) — Team leader : **Joëlle Chabry**

Page 19

- Appreciation on the results:

"Nearly half of the published papers are devoted to a topic abandoned by the group"

The only abandoned project is the one involving the use of biotinylated recombinant PrP corresponding to 2 out of the 8 published papers. The reasons of the end of this scientific axis have been clearly explained in the submitted application. Indeed, due to the reduction of technical staff, we decided to refocus our plans for the sake of efficiency. **We would appreciate the modification of this point in the final report.**

Page 19

- Appreciation on the results:

"The training of 3 PhD students during a 5 years' period is also fair but far from outstanding"

It should be noted here that the team leader is the only staff with a HDR or similar grade required to train Ph.D students. The current regulation of our "Ecole Doctorale" does not allow the training of more than 3 students per HDR at the same time. Thus, the team leader has supervised the maximum number of PhD students over the last 4 years. **We would appreciate the removal of this sentence from**

the final version of the report.

Page 20

- Appreciation on the strategy, management and life of the team:

"This is a relatively small group, with 3 personal now, and with 7 expected recruits in the next 4 years"

The expected recruitments are not 7 but 2 as indicated in the table.

Page 20

- Appreciation on the strategy, management and life of the team:

"No any evident initiative aiming at scientification animation was recognised in the strategy planning, which seems to be urgently required to bolster the group's performance"

The point raised here is unintelligible. **We think that this sentence could be removed from the final version of the report.**

Page 20

- Appreciation on the strategy, management and life of the team:

"The understanding is that teaching duties come very low in the priorities of the group, to such an extent that this aspect is not commented in the planning of activities"

The "teaching activities" part was indeed filled up in the application file but may have been missed by the reviewing committee. It should also be noted that the team leader is a member of the "Ecole Doctorale" of the University of Nice since 2006, does Master training courses since 1999 and has participated seven times to PhD theses and HDR committees over the last 4 years. Dr. Zsürger, the team engineer, assures Master training courses since 2005 at the "Ecole Polytechnique Universitaire" (25 hours/year). Since 2010, Dr. Petit-Paitel teaches Biological Sciences to graduate and Master students at the Skema International business school (40 hours/year). **Again, this statement should be corrected in the final version of the report.**

Point-by-point comments to the team E10's report (Mechanisms of gene regulation in physiopathology) Team leader : **Enzo LALLI**

Page 29

- Appreciation on the results:

"The research activities of this team are focused on the role of SF-1 (the nuclear receptor stereoigenic factor-1) dosage in the pathogenesis of adrenocortical tumors and development of therapeutic strategies, including precilical trials using novel drugs targeting beta-cathenin pathway (inhibitors of beta-catenin), SF-1 inverse agonists and MTOR inhibitors. The team is also investigating the role of transcription factor Dax-1 in mouse embryonic stem cells and in the pathogeny of Ewing tumors in human, and the role of the Task1 potassium channel in regulating functional zonation of the adenal cortex. The research performed seems solid, but not particularly innovative or exciting"

I strongly disagree with the conclusions made in this part of the report about the significance of our research. I believe that the originality of our work and of the approaches we have taken to dissect several aspects of adrenocortical physiology and pathology were not appreciated in proportion to their real quality. I would like to suggest that this is probably due to the fact that unfortunately the composition of the committee was strongly biased towards experts in neurobiology but no expert in the fields of

endocrinology and oncology (not to mention the more specific domain of our expertise, the adrenal gland) was present. In my view we have made seminal contributions in the field, in particular by demonstrating for the first time the pivotal role of transcription factor SF-1 in the pathogenesis of adrenocortical cancer, the role of potassium channels in shaping adrenocortical functional zonation and of certain miRNAs in regulating the IGF/mTOR signalling pathway, which also has a very important role in cancerogenesis. One indicator of the importance of our work on SF-1 and adrenocortical cancer is that, for this discovery, I was awarded the prestigious "Cancer" prize from the French Academy of Medicine. I am trustful that all colleagues working in our field may confirm the innovative character of our research and the impact that it had in the domain. **For these reasons, I ask that the sentence *"The research performed seems solid, but not particularly innovative or exciting"* be changed.**

Page 29

- Appreciation on the results:

"The research activities of this team led to contributions in 27 publications (between 2006 and 2010), and 5 reviews, which is about 2 publications per researcher per year, above average. The publications are in general not in high profile journals, but some are reasonably well cited"

This is an understatement. During the period cited, our group has published several papers in the best journals in the domains of endocrinology (J. Clin. Endocrinol. Metab., Mol. Endocrinol., Endocrinology) and oncology (Cancer Res., Stem Cells, Oncogene), plus a great number of invited reviews, which again demonstrates the impact that our activity has in the field. Furthermore, if we look at the specific number of citations of our publications using an easily accessible tool like the ISI Web of Science, we will see that many of them approach or exceed the impact factor levels of some of the most important generalist journals (e.g. our 2007 Mol. Endocrinol., paper has 39 citations; our 2007 Cancer Res. paper has 36 citations; our 2008 JCEM paper has 14 citations; our 2008 EMBO J. paper has 28 citations, and so on). **For these reasons, I ask that the sentence *"The publications are in general not in high profile journals, but some are reasonably well cited"* be revised.**

Page 29

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners:

"The PI received an award from the academy of science. He is frequently invited to talk, in particular in international events.
The group is of a reasonable size, the number of full time researchers is high. The recruitment of a new researcher somehow can be seen as a success, although it is not clear at all how she fits in the themes of the group"

This is not entirely exact. Apart from the integration of Dr. Demolombe into our group (see specific comments below), we also succeeded to recruit Dr. Doghman to the very competitive position of a tenured CNRS scientist. Dr. Doghman started her post-doc in our team in 2005 and was recruited into CNRS in 2009. I consider this as an institutional recognition of her brilliant career inside our team, which led her to publish 10 papers in the 2005-2010 period, most of which as a first author. **For these reasons, I ask that the sentence "*The recruitment of a new researcher somehow can be seen as a success*" be revised.**

Page 29

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners:

"The group raised about 1 M Euros in 4 years, from various sources including international ones. The PI coordinates several research projects, including international ones"

Our current funding situation is in or above the average of the other IPMC groups, while international collaborations of our team, which are encouraged in the AERES report, are probably in the top part of the institute list.

Page 30

- Appreciation on the project:

"The proposed project is in continuation with previous work. It includes analysis of mechanisms of transcriptional regulation by SF-1 and DAX-1, preclinical studies of novel drugs on tumor cells. Research activities are also extended to the role of TASK potassium channels in adrenal function zonation and pathophysiology of hypertension, and study of the relation ship between gene expression and mechanical stress. It would not be a problem if the current research was cutting edge or on the forefront."

I hope that at this point I have demonstrated how well our research is positioned in the field. **For these reasons, I ask that the sentence *"It would not be a problem if the current research was cutting edge or on the forefront"* be revised.**

Page 30

- Appreciation on the project:

"As it stands and in view of the previous results and contribution, the proposed project appears conventional with no real originality. It is also difficult to expect significant breakthroughs from the proposed investigations"

I would like to remark here that our projects, contrarily to what is stated here in the report, are indeed situated at the cutting edge of the current international research in several fields of adrenocortical pathophysiology. This is best shown by the fact that all of them are currently funded by some of the most important French and international funding agencies: Institut National du Cancer, ANR, FP7 (encouragement to participate more actively to European funding programs is one of the main recommendations that the committee made for our institute) and NIH. For these reasons, as well as for the reasons explained above, **I ask that the whole sentence *"As it stands and in view of the previous results and contribution, the proposed project appears conventional with no real originality. It is also difficult to expect significant breakthroughs from the proposed investigations"* be revised.**

Page 30

- Appreciation on the project:

"Translational part of the project may appear potentially interesting. However, it is not clear why the PI and his team want to pursue these investigations"

I thought I had sufficiently explained in the Project part of our application (even if forcedly concisely for allowed space reasons) our choice to invest into the preclinical testing of novel drugs for adrenocortical cancer. I can reiterate it here: "Therapeutic results are in fact still poor in this type of cancer and the need exists to develop new drugs which are more active towards the tumor and less toxic for the patient". I just wish to add that unfortunately adrenocortical cancer is still a deadly disease and there is strong and urgent need for novel, more active drugs. Our studies have indicated novel, potentially relevant

therapeutic targets that we wish to investigate in detail in our future studies. For these reasons, **I ask that the sentence "However, it is not clear why the PI and his team want to pursue these investigations" be revised.**

Page 30

- Appreciation on the project:

"The choice concerning new projects is also not well justified, including its integration to the other projects. The project developed by the new researcher, concerning the regulation of gene expression by mechanical stress in cardiomyocyte, is completely disconnected from the rest of the group. Although we understand the reasons of her arrival, it should be made sure it is a strength and not a cause of unfocussing"

I appreciate these constructive observations from the evaluation committee. Of course, since the time of the first discussions about Dr. Demolombe recruitment to the IPMC, we also felt that it is important that she integrates productively into our team. I see her contribution as a strength to extend our competence in a different field of the broad domain of gene regulation and not as a weakness. We have decided to join our forces and to take the risk of pursuing new, innovative projects. She takes advantage of her relocation to develop a new aspect of her research related to mechanical stress and gene transcription. In particular, she will investigate the role of direct transmission of mechanical stress to the nucleus in the regulation of ion channel transcription, focusing on the role of desmin, lamin A and emerin. She also wants to explore the role of a novel protein called Piezo1 (Science 330: 55, 2010), an essential component of mechanotransduction. Her projects are highly innovative, with great potential for identifying new pharmacological targets for the treatment of the most common cardiac diseases, i.e. heart failure and atrial fibrillation. Our experience is certainly an additional advantage for her success. However, I completely agree with the committee about the need to keep the research pursued by Dr. Demolombe as focused as possible and for this reason she will take great advantage from the collaboration with other IPMC teams, in particular with the one directed by Dr. Honoré (reinforcing internal interactions is another of the main recommendations made by the committee). I would like to remind here that Dr. Demolombe has always been a very productive scientist (51 publications, 7 as last author; H-factor: 24), leader in her field. She is funded by the prestigious Leducq Foundation, which is probably the most selective funding agency in the cardiovascular field, and is also an appointed member of the INSERM scientific council. In summary, I believe that the integration of a scientist with the experience of Dr. Demolombe at the IPMC represents an added value for the whole institute and I will be happy to continue hosting her in our team. However, discussions about the continuation of her activity in our team are in process and a decision will be taken within six months from now. **For these reasons I ask that the sentence *"The choice concerning new projects is also not well justified, including its integration to the other projects. The project developed by the new researcher, concerning the regulation of gene expression by mechanical stress in cardiomyocyte, is completely disconnected from the rest of the group. Although we understand the reasons of her arrival, it should be made sure it is a strength and not a cause of unfocussing"* be revised.**

Page 30

- Conclusion:
  - Summary:

"This team has a good past scientific production relating to pathogenesis of adrenocortical tumors and transcription factors. The projects are however a bit unfocussed and not very enthousiastic in view of the international competition"

I maintain that the diversity of our projects is our strength and at the forefront of international research. **I ask then that the sentence *"The projects are however a bit unfocussed and not very enthousiastic in view of the international competition"* be changed.**

Page 30

- Conclusion:
  - Strengths and opportunities:

"Good expertise in the field of adrenocortical tumors. Good scientific production (quantitatively). Diverse collaborations"

See my comments above about the relevance of our scientific production. **I ask then that the sentence *"Good scientific production (quantitatively)"* be changed as follows: *"... quantitatively as well as qualitatively"*.**

Page 30

- Conclusion:
  - Weaknesses and threats:

"Dispersion. There is a lack of sharpness in identifying the major research questions"

We have already shown in the past our capacities to successfully pursue different, and potentially disparate, research projects. There is no reason why we should fail to do so in the future provided sufficient funding is assured. See also my comments above about the introduction of new themes into our research projects. **I ask than that the sentence *"Dispersion. There is a lack of sharpness in identifying the major research questions"* be changed.**

Page 30

- Conclusion:
  - Recommendations:

"The team should focus the project on the group's field of expertise and make a better use of IPMC facilities to be more ambitions and broaden the approaches used. Past activity justifies trusting the continuation of the group activity but the panel was not very enthusiastic with the projects proposed in term of long term competitiveness and pertinence. The translational part of the project may appear potentially interesting. However, it is not clear why the PI and his team want to pursue these investigations"

See my comments above about the relevance of our projects and the justification of our translational studies. **I ask than that the sentences *"the panel was not very enthusiastic with the projects proposed in term of long term competitiveness and pertinence"* and *"However, it is not clear why the PI and his team want to pursue these investigations."* be changed.**

Point-by-point comments to the team E12's report (**Molecular Physiology and Physiopathology of Ion Channels**) Team leader : Florian LESAGE

<u>We suggest to remove or at least modify the following points</u> that are not supported by facts or reflected misunderstanding of the submitted documents:

Page 33:	Page 34:

• **Appreciation on the results…**	• **Conclusion** ○ **Weaknesses and threats**
" ***<u>Although modest in number</u>, the quality of the papers is very high to excellent (...)***"	"***<u>The number of papers could be higher</u> given that 3 inserm/cnrs researchers were present in the team.***"

The team has produced 11 publications - 3 reviews and 8 original articles (1 Cell, 2 PNAS, 2 EMBO J, 2 J of Neuroscience, 1 JBC) - 9 of them with the team leader as senior author and 7 of them with a team member as first author. The committee may have noticed that one of the CNRS researchers was on sabbatical from July 2009 to the next summer for acquiring new expertise. During this period, he has published as first author one more article in PNAS and one in Nature Communications. This raises the production of the 3 permanent researchers to 10 original articles in excellent to top journals and 3 reviews. For a team of 3 researchers and two PhD students, this production is not modest. **We would really appreciate if the negative terms describing the team productivity were removed from the report: "*Although modest in number*" in the first sentence and the complete second sentence.**

Page 33:

- **Table**
  - **N3-past:** should be **<u>0</u>** instead of **<u>1</u>**

S Feliciangeli who was initially post doc became Inserm CR2 in 2007 and is included in N2=3 (full time researchers from research organizations: F Lesage, G Sandoz and S Feliciangeli).

Point-by-point comments to the team E13's report **(Ion channels and pain)** Team leader : Eric LINGUEGLIA

page 35

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

"In contrast, the capacity to attract post-docs and students during the last 4 years is weak (only 1 graduate student and 0 post-doc during this time)"

We would like to point out one error on the number of students and post-docs who have joined the lab during the last 4 years. As mentioned in the oral presentation, **we have actually attracted during this period 5 graduate students** (i.e., Master students) **and one visiting scientist** from the University of Barcelona (12 months).

The unique graduate student listed in the comment has probably been collected from the Results section of the IPMC written report, which was only listing students present in our team by June 30, 2010 and was not mentioning the former Master students who have joined our lab over the entire 4-year period.

Point-by-point comments to the team E15's report (Activity-dependent dynamics and roles of synaptic SUMOylation) Team leader : **Stéphane Martin**

The leader of Team E15 would like to thank the committee for their productive comments.

<u>Page 39</u>

- Appreciation on the results

«*There seems to be an agreement on the splitting on the sumoylation theme with the original laboratory*».

This sentence may erroneously reflect the fact that our research projects emerged from the original lab. Although we are both interested in synaptic sumoylation, the projects developed in my laboratory are entirely novel. However, it is true that we have an agreement with this laboratory to avoid working on the same target proteins. I kindly ask the committee to amend or remove this sentence from the report.

Point-by-point comments to the team E17's report **(Genomics and Evolution in Neuro-Endocrinology)** Team leader : Jean-Louis NAHON

Page 43

- Appreciation on the impact…

« The recruitment seems to be low, maybe due to limited funding(…)It is not clear that they reflect the ability of the PI to raise money ».

Criticisms regarding the *"recruitment (that) seems to be low, may be due to limited funding…"* and the fact that *"two of the three big grants have been obtained in collaboration. It is not clear that they reflect the ability of the PI to raise money"* are, at best, reflecting misunderstanding of the submitted documents or, more unexpected, lack of knowledge regarding the mechanisms of the granting process in France and Europe that, until very recently, were based on collaborative projects. During the last four years I, and I use this pronoun on purpose, raised roughly 1 113 000 € from EU grant (WP2 I led alone…and in many times I took the leadership in driving the APES contract as the CNRS DR20 staff could confirm it), ANR-MNP grant (I am the "Coordinator" and collaborate with the team of E. Bezard who is partner 2), CNRS-Hôpital Laval (Québec) (PI of a project made in collaboration with D. Richard), CNRS-INSB "Biothèque Primate" (PI of the project at the IPMC). I also obtained supports from the French Medical Research Foundation/FRM (as member of the Scientific Council) and France Parkinson Association (only 100 K€ in total). In addition I strongly urged other senior members of the team to participate to the exalting funding race and Alice Guyon (CR1 CNRS) also succeeded in obtaining financial supports from the "Fondation de France" and CNRS-INSB (a highly competitive PEPS contract), and Gregory Conductier (Post-doctorant) has recently received the french "Société de Nutrition" Award with joined financial support. With this funding, I have recruited 6 engineers and 3 post-doctoral fellows for time periods in between 2 to 4 years as well as 10 graduate students (the information was indicated in the § Main Achievements). The ability to raise more than 1 million euros within 4 years and to recruit for the necessary projects up to 11 engineers/researchers (including two PhD students on MESNR funding) positioned our team in the top level of the funding "collectors" and non-permanent fellow "recruiters" at the IPMC.

Page 44:

- Conclusion
  - Weaknesses and threats

"The mechanism for general allocation of resources is unclear"

This sentence at this place of the report is not clear. We do not understand the point raised here and we believe that it can be removed from the final version of the report.