LP2M - Laboratoire de physiomédecine moléculaire

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Laboratoire de Physiomédecine Moléculaire

From the

University of Nice Sophia Antipolis

CNRS

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Le Président de l'AERES

Didier Houssin

Section des unités de recherche

Le Directeur

Pierre Glorieux

February 2011

Research Unit

Name of the research unit : Laboratoire de Physiomédecine Moléculaire

Requested label : UMR CNRS

N° in the case of renewal : CNRS UMR 6097

Name of the director : Mr Jacques BARHANIN

Members of the review committee

Committee chairman

Mr Rodolphe FISCHMEISTER , University Paris Sud, Chatenay Malabry, France

Other committee members

Mr Aleksander EDELMAN, University Paris Descartes, Paris, France

Mr Dominique EMILIE, University Paris Sud, Clamart, France

Ms Pascale GUICHENEY, University Pierre et Marie Curie, Paris, France

Mr Bertrand LAMBOLEZ, University Pierre et Marie Curie, Paris, France (CNRS)

Mr Arthur WILDE, University of Amsterdam, Amsterdam, Netherlands

Observers

AERES scientific advisor

Mr Pierre LEGRAIN

University, School and Research Organization representatives

Mr Jean-Marc LARDEAUX, University Nice Sophia Antipolis

Mr Alain DOUCET, CNRS

Report

1 • Introduction

- Date and execution of the visit

The visit took place on February 17, 2011, in the laboratory. The visit was well prepared. All members of the review panel received before the site visit the necessary scientific and administrative documents for the evaluation of the scientific activity of the Unit and its project. Although the writing of the scientific document was not optimal, the site visit was well organized and clarified most of the interrogations raised by reading the documents.

The time schedule was perfectly followed. After the scientific presentations were made by the past director of the research unit and the team leaders, the expert review panel met with the different staff categories: i) PhD students and postdoctoral fellows; ii) engineers, technicians and administrative assistants; iii) researchers with permanent positions. Finally, the panel met the representatives of Nice Sophia Antipolis University and CNRS.

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

The present project (5 teams, ~25 people) originates from the laboratory "Transport Ionique Aspects Normaux et Pathologiques", created in January 2008 (CNRS FRE3093 from 2008 to 2010 and then administratively attached to UMR 6097 "Institut de Pharmacologie Moléculaire et Cellulaire" (located in Sophia Antipolis) from 2010 to 2012. It is located on the Science Valrose Campus at the University of Nice Sophia Antipolis. Prior to 2008, the teams of Michel Tauc (Team 4) and Laurent Counillon (Team 3) were part of the laboratory of "Physiologie cellulaire et moléculaire des épitheliums et des compartiments calciques" (UMR CNRS 6548 in Nice, directed by Philippe Poujeol). Said Bendahhou (Team 2) and Jacques Barhanin (Team 1 and Unit director) were at the "Institut de Pharmacologie Moléculaire et Cellulaire" (UMR 6097 CNRS) in Sophia Antipolis. Claudine Blin-Wakkach (Team 5) was in the laboratory "Génétique, Physiopathologie, et Ingénierie du Tissu Osseux" (UMR CNRS 6235 in Nice, faculty of medicine, directed by Georges Carle). In 2010, C. Blin-Wakkach and A. Wakkach moved to an INSERM unit (U576, Nice) to emerge as an independent group. They now joined with M. Rouleau, coming from another INSERM unit (U898, Nice), to constitute a 5th team in this project.

Although some of the groups have collaborated in the past (prior to 2008), this is a relatively new laboratory, with a rather short common history.

- Management team

The former director (Laurent Counillon) is very active in the University of Nice Sophia Antipolis and has obtained clear recognition for the large effort he developed to build this group. The new Director (Jacques Barhanin) is perhaps less keen at administrative management but has an outstanding international recognition and is clearly a scientific leader of the unit. The previous AERES committee report (March 2009) invited "the group leader of Team 1 to deeply commit himself in the scientific and human life of the unit", which he clearly did by taking now the leadership of the unit. The relationship between the director, the individual team leaders and the staff is excellent, with great confidence and pleasant working atmosphere. This is a warranty for the unit to function smoothly and in a good spirit. The management team has already been able to attract a new team (Team 5) which is a good sign for the future development of the unit.

- 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)	4	4
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	6	9
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)	4	4
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1	
N6: Number of Ph.D. students (Form 2.7 of the application file)	7 (+3)	
N7: Number of staff members with a HDR or a similar grade	8(+2)	13

2 • Overall appreciation on the research unit

- Summary

This unit is composed of five teams and altogether about 25 people. They occupy a lab space of 600 m², which will soon need to be expanded if they want to attract more people. Common interests within the unit are ion channels and transporters, pH regulation, volume regulation, reactive oxygen species, inflammation, with a continuum from genes to animal in vivo studies. In general, the committee found the project of the laboratory attractive, ambitious and realistic. The production during the past 4 years has been on average good to very good, with a total of 67 publications since 2008, including 7 in journals with impact factor >8 (1 Cell, 3 PNAS…). The leader of the laboratory is a first rank international scientist who has established an efficient collegial management. The group has demonstrated in the past a large capacity of raising financial resources.

- Strengths and opportunities

An ambitious project to generate a critical mass in the field of integrated physiology in Nice, with complementary skills (ion channels and transporters, inflammation) and opportunities for translational research (transplantation). The team 5 will add strength and new potencies to the research group. The group has demonstrated in the past 2-3 years a great capacity to raise funds (150 k€ total budget in 2008, 600 k€ in 2011).

The University representative has indicated a strong political decision to help this unit to develop by opening two new faculty positions (at professor or MCF level) for this unit.

- Weaknesses and threats

Two large units are already established on the Science Valrose Nice campus: the CNRS UMR 6543 « Institut de Biologie du Développement et Cancer" and the INSERM UMR 636 « Génétique du développement normal et pathologique ». The University of Nice Sophia Antipolis has the project to federate these two units and this new "Laboratoire de Physiomédecine Moléculaire" to create a unique "Biology Research Center" within the next 3-4 years. This will only be possible if this new laboratory is securely funded and labelised.

The number of PhD students and postdocs is presently rather limited. While the unstable current administrative situation of the unit is partly responsible for this, as soon as the unit is institutionally labelised, it will have to invest part of its external budget to attract more young fellows.

Although the unit is small (less than 25 people), it proposes a division in 5 teams. This division results in teams that are small and hence fragile.

- Recommendations

Additional space should be provided by the University to the unit for team 5 and for future growth of the unit.

The small size of the teams requires careful central management to promote recruitment of young postdocs and permanent researchers which is the only way to strengthen and stabilize them over the next 4-year period.

Support from the university and CNRS is also needed to increase the number of technical staff, which is currently limited to secretarial work and animal facilities.

- Production results

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	4
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	6 (+3)
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	1
A4: Number of HDR granted during the past 4 years	4 (+2)
A5: Number of PhD granted during the past 4 years	4 (+1)

3 • Specific comments

- Appreciation on the results

The laboratory is composed of 5 teams, 4 of which were already part of the same structure since 2008, and the 5th one (team 5 – C. Blin-Wakkach) joining the laboratory in 2012. As a whole (5 teams), the laboratory has produced 67 publications in international journals: 2 Cancer Res (IF=7.5), 3 PNAS (9.4), 4 JBC (5.5), 5 Cell Physiol Biochem (3.5), 1 Horm Metab Res (2.7), 6 Am J Physiol (3.9), 1 Cell Biochem Biophys (2.3), 4 J Cell Physiol (4.3), 2 J Immunol (6.0), 1 J Interv Card Electrophysiol (1.1), 2 J Neurosci (7.5), 1 Philos Trans R Soc Lond B Biol Sci (5.6), 2 PLoS One, 1 Free Radic Biol Med (5.4), 2 Pflügers Arch (3.5), 1 J Am Soc Nephrol (7.5), 1 Hypertension (7.4), 1 Diabetes (8.4), 2 Stem Cells (7.7), 1 Embo J (8.7), 1 Biochemistry (3.4), 1 Endocrinology (5.0), 1 BBRC (2.7), 1 Neuroscience (3.6), 1 Blood (10.4), 1 Cell (31.3), 1 Hum Mol Genet (7.3), 1 BBA (4.0), 1 Heart Rhythm (4.4), 1 Cell Mol Neurobiol (2.6), 2 Biol Cell (3.4), 1 Cell Mol Neurobiol (2.6), 2 Synapse (2.6), 1 Psychopharmacology (3.7), 1 Neuropsychopharmacology (6.8), 1 Cell Cycle (4.1), 1 C R Biol (1.5), 1 Ann Med (5.4), 1 Mol Microbiol (5.2), 2 FASEB J (7.1), 1 Bone (4.2), 1 Exp Hematol (3.2) and 1 Cell Death Diff (7.6).

While the number of outstanding publications is relatively limited (7 publications with IF>8, including 1 Cell and 3 PNAS), the average publication level is good, with a mean impact factor of 4.6.

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

32 invitations to meetings (L. Counillon, 10 ; J. Barhanin, 8 ; C. Blin-Wakkach, 6; C. Duranton, 1; S. Bendahhou, 1; others, 6), with a majority (19) in France. International recognition is highest for the Unit leader (J. Barhanin).

Although their total number is too low, all PhD students currently in the lab (total of 3 in 2010) are from abroad. The last recruitment of a permanent researcher was in 2007 (Team 3). Yet the unit was able to attract a new team (Team 5) which brings in 3 full-time researchers.

The Unit as a whole has been quite successful in raising funds from various sources (ANR, AFM, INCa, VLM…). In the past two years, institutional funding (CNRS and University) represented on average 84 k€/year, and 348 k€/year were additionally raised on specific projects.

Each team has its own set of active national and international collaborations. Few PIs (M. Tauc, L. Counillon, J. Barhanin, C. Duranton) have served in organizing committees of various scientific meetings or in expert panels.

Four patents have been (and one is currently being) filed since 2006. The group of M. Tauc participates in an "ANR emergence" project on hypoxic tolerance in small bowel transplantation.

- Appreciation on the management and life of the research unit

There is an efficient internal communication through weekly organized lab meetings allowing informal scientific presentations and discussions. Major decisions (new equipments, funding, recruitment, etc.) are taken in a transparent manner on the basis of open dedicated discussions.

The management team takes about 30% on each individual grant to spend on new equipments (either common or for individual projects) as well as on new emerging projects.

Altogether, four members of the unit have university faculty positions. The former unit director is particularly involved in teaching and in other university activities (Ecole Doctorale). Through teaching and training of young fellows, the whole unit contributes to the "revival" of Physiology in the program studies of the Faculty of Science of the University of Nice Sophia Antipolis.

Collective rules have been installed concerning funding: 1) up to one-third of each contract contributes to the common expenses and equipment of the unit; 2) any group with a temporary lack of funding is supported temporary by the Unit.

- Appreciation on the scientific strategy and the project

Although the document provided to the committee is poorly written, the oral presentations were clear and convincingly showed a strong coherence and complementarities between the teams, and scientific perspectives for the unit as a whole. As illustrated by the specific projects presented in the individual team reports, the five teams share common interests with complementary expertises on ion channels and transporters, pH regulation, volume regulation, reactive oxygen species and inflammation. Several organs (brain, muscle, heart, bone) and cell types are being studied, with a continuum from genes to animal in vivo studies.

4 • Appreciation team by team

4.1.Team 1 : Ion Channel Genetics

Team Leader : Mr Jacques BARHANIN

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)		1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)		1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)		
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		0
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		
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

- Appreciation on the results

Jacques Barhanin is internationally known in the field of the potassium channels and developed numerous national or international collaborations. One of his most important contributions was the discovery in 1996 of a new class of K+ channels with two pore domains and four membrane-spanning helices, active as dimers. He is working on the physiological role of this family of genes, TASK1 to 3, either in heterologous expression systems, or in animal models.

During the last four years, they produced mice invalidated for the 3 TASK channel genes task1 (kcnk3), task2 (kcnk5) and task3 (kcnk9) and double KO task1-3 and task2-3.

Important original contributions on the role of these channels have been done, showing:

the role of task2 for K+ efflux in proximal tubule cells during hypo-osmotic shocks (2 publications);

the absence of task1 led to primary hyperaldosteronism associated with abnormal adrenal cortex functional zonation (1 major publication in EMBO J);

a specific expression of task2 in the retrotrapezoid nucleus (RTN), which plays a pivotal role for pCO2 and pO2 sensing, and a lack of hypoxic ventilatory depression and resetting of the CO2 sensitivity in task2-/- mice (1 major publication in EMBO J).

In addition, the team leader is co-author of other reports on:

the functional characterization of two K+ channel mutations causing long QT syndrome

the role of KCNE3 in intestinal and tracheal Cl- transport using kcne3-/- mice.

From 2006 to 2010, the team contributed to one review and 17 original publications in high impact journals, including 3 with the team leader as senior author, and 7 as penultimate author.

The team leader has been invited to several international meetings, and he co directed a thesis.

- 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 small as it is composed of Jacques Barhanin, a researcher with teaching duties (MCU), a PhD student, and a technician paid on an ANR grant.

The team leader has numerous collaborations with French teams, especially with previous local colleagues, and international teams.

The team has a good funding, from the region (Respitask 2008), and the ANR (genopat 'Hypertask', 2009-2011). There is also a funded collaboration with a German laboratory (2008-2011).

A patent has been filed on « Process of screening of drugs used for treating respiratory problems ».

- Appreciation on the scientific strategy and the project

The first project focuses on the role of TASK K2P channels in adrenal gland functional differentiation and control of aldosterone secretion. They expect to find new pathways/proteins and identify genes which could be mutated in humans and cause primary hyperaldosteronism (collaboration with a laboratory in Paris). If mutations are found, the team will perform functional analysis in primary cultured adrenocortical cells and identify the dysregulated signaling pathways. This project may appear risky but some interesting leads have been identified.

They will explore the role of TASK3 in aldosterone secretion using task3-/- mice on various diets, and develop an adrenal slice preparation to perform electrophysiological recording and calcium imaging. They will also further explore the mechanisms leading to aberrant adrenal functional zonation in task1-/- mice linked to sex hormones, this is based on preliminary data showing differentially expressed transcripts in adrenal glands of female task1 mutant mice as compared to wild type.

The second project is on central O2/CO2 chemosensing via TASK K2P channels and its role in respiratory pathophysiology. It is based on published observations of this team (PNAS 2010) that i) TASK2 channels are candidate O2/CO2 sensors via intracellular ROS/pH, respectively, ii) TASK2 channels are selectively expressed in retrotrapezoid nucleus (RTN) neurons whose genetic ablation causes congenital central hypoventilation syndrome, and iii) TASK2 deficient mice exhibit central respiratory deficits. This project, coordinated by this team, additionally involves highly regarded experts in respiratory physiology and in mouse genetics and development. This team will perform patch-clamp experiments in brainstem slices of available mutant mouse lines to characterize the role of TASK channels in RTN neurons chemosensitivity.

This original project has far-reaching fundamental and translational implications in the understanding of respiratory central networks and of neonate respiratory distress as well as adult sleep apnea.

The two projects are funded and collaborations are set up.

- Conclusion :

  - Summary

These are two interesting and original projects on K+ channels based on available mutant mice and linked to human pathologies.

  - Strengths and opportunities

Both projects are funded with collaborations already in place.

The team leader has a solid experience in physiology of K+ channels and management of murine models.

The team leader has the capacity to develop new collaborations with French and international researchers if necessary.

– Weaknesses and threats

The team is small and without young full-time scientists so far

– Recommendations

A postdoctoral fellow expert in patch-clamp analysis in tissue slices should be recruited. If securely funded and affiliated as a CNRS UMR instead of the current transitory administrative situation, this team should be able to attract more PhD students and post-doctoral fellows.

4.2.Team 2 : Ion channels in nervous, muscular and cardiac disorders

Team Leader : Mr Said BENDAHHOU

- Staff members

	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)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)		
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		
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

The research group headed by Said Bendahhou is small and according to the title focuses on "Ion channels in nervous, muscular and cardiac disorders". He was working in the group of Jacques Barhanin until recently, and has his own subject. They decided to divide the team in two to follow the recommendations of the last AERES committee (March 2009) who recommended "encouraging CR1 researchers to affirm their scientific personalities". This may be a bit premature since these two teams are small and had, until now, no clear long term perspective owing to the transitory situation of the unit.

The main personal topic of the team leader is 'Andersen-Tawil syndrome (ATS)" and because the only ion channel known to be causally involved at present, i.e. IK1 encoded by KCNJ2, is expressed in both cardiac and skeletal muscle this disease entity fits well into the general topic of the research group. It has to be acknowledged, however, that this topic is rather narrow. Furthermore, since the initial major findings shortly after the discovery of the first mutations in KCNJ2 in 2001, limited progress has been made. Nevertheless, the team leader is an expert in electrophysiology, he performed studies of the mutants in human skeletal myoblasts and developed muscle physiology after adenoviral transfection. The project on the deterioration mechanisms of excitation-contraction coupling leading to paralysis or myotonia is interesting and relevant according to the skills of the team.

Since 2006, the team leader contributed to 8 publications, with 5 in either first, last or penultimate author (1 Cell as first coauthor and 1 Hum Mol Genet as 1st author in 2007). The overall modest scientific visibility of the team leader (h factor of 20) is probably a reflection of the rather narrow scope of his research and the small size of his group.

Another researcher (with teaching duties) is part of the group only since 2010. Her previous track record was reasonable with a couple of nice papers in the neuroscience literature but since 2008 only one manuscript has been published.

The research ideas in this program are worth while to explore and it is to be expected that they may certainly contribute to further knowledge in this field. Patients are waiting for further insight into the pathophysiological basis of their disease where particularly the skeletal muscle complaints are difficult to treat. A significant part of the research plan is directed to the role of muscle excitation-contraction coupling. Whether this program will be able to identify new genes is uncertain. This is a worldwide effort and details of the number of patients without an already identified KCNJ2 mutation are not given.

The quality and stability of partnerships seems sound. This is important since they don't see the patients themselves. relying for new patients' material (biopsies, new mutation) on their collaborations.

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

The number of awards of this group, including invitations to international symposia, is relatively low. Team members have been invited to national meetings 4 times and to international meetings 4 times. It is unclear whether this includes submitted abstracts. Awards, excluding the above mentioned invitations, have not been obtained.

Funds have been obtained from AFM and on a collaborative basis from ANR (Hypertask).

No post docs neither guest scientists have been attracted.

This research has socio-economic implications to ATS patients who desperately are in need for new treatment modalities.

- Appreciation on the scientific strategy and the project

As stated, the research questions themselves are worthwhile to address and the group will certainly be able to address some of them in the 4 years to come. However, it seems that the size of this group is too small to act as an efficient research group. Research output has not been very significant in the last few years and no change may be easily foreseen in the years to come. Furthermore the complete dependence on clinical groups at distance (as far as new material is concerned) is a weak link, despite the stable relationships that appear to be present over the past years.

- Conclusion :

  - Summary

The proposed research group is small and has, thus, a limited focus. In the initial years of the identification of the role of KCNJ2 and the protein/current it encodes for the group was at the forefront of this research but in the last years the output has somewhat decreased. Their best work dates to the years before 2008. This is also reflected in the number of citations to their most recent work.

  - Strengths and opportunities

The strong focus can be regarded as a strength and the research question are worth while to be addressed. Insight into the pathophysiology of this disease will certainly be of benefit to ATS patients who desperately are in need for new treatment modalities. Within the proposed research programm there is a line of research devoted to excitation-contraction coupling in skeletal muscle and that line certainly has the opportunity to lead to interesting new data. More collaborations can be developped. It is noteworthy that the team leader is an expert in electrophysiology, and due to this expertise, he should be able to develop collaborations with the other teams of the laboratory and other groups.

– Weaknesses and threats

The size of the group is small. This size, limited funding and the lack of significant scientific output in most recent years is a serious weakness and threat.

The complete dependence on clinical groups not in the neighborhood of their institute is a threat. This is important because new patient material, both biopsies and new patients without KCNJ2 mutation, have to come from them.

– Recommendations

Given the small size of this team, one could recommend to fuse this group with one of the other groups, the most logical being Team 1. This would enlarge the focus of research to a larger spectrum of potassium channels and to a larger spectrum of disease entities. The latter are also of much larger clinical importance than ATS. However, as the previous AERES committee two years ago recommended to encourage CR1 researchers to affirm their scientific personalities, perhaps one should give a chance to this young team to build up on the grounds of the solid existing internal collaborations.

4.3.Team 3 : Proton Dynamics in cellular and intracellular compartments

Team Leader : Mr Laurent Counillon

- Staff members

	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)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)		1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		
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

It is noteworthy that the team leader is the current unit director, but will be relieved of this charge after the renewal of the unit. The team is specialized in the molecular physiology and biophysics of proton transporters and intracellular pH regulation, and internationally recognized in this field. Indeed, the team made several key contributions to the characterization of the ubiquitous sodium/proton exchanger NHE-1 by showing that NHE-1 activation by protons involves a MWC cooperative mechanism and is regulated by growth factors (EMBO rep. 2004) and that NHE-1 is sensitive to membrane tension resulting of osmotic pressure or membrane composition (Biochemistry 2008, J Cell Physiol 2008). Recently, they demonstrated that the antineoplastic drug cisplatin inhibits NHE-1 as well as mechanosensitive channels, via an effect on the plasma membrane (Cancer Res 2010). This latter finding has received a broad attention since it provides insights into the side effects of cisplatin.

Six peer-reviewed papers were published since 2006 in very good/good journals (Cancer Res X 2, Endocrinology, J Cell Physiol…), as well as a review article and two book chapters. Thus, the production is very good considering the team's size and team leader's additional commitments to unit directorship and teaching.

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

The team's national and international visibility is assessed by regular invitations to national and international meetings/seminars. One PhD thesis has been supervised during the last four years. The team has been successful in getting national and local financial support for the next three years.

The team compensates a small size through productive collaboration with academic partners (local, national and international). This allows ambitious projects to be achieved (NHE-1 regulation by membrane tension/composition, effect of cisplatin) and proposed (see below). Postdoc recruitment on available funds will compensate for the loss of a staff technician.

- Appreciation on the scientific strategy and the project

The project maintains the focus on proton transporters and proposes ambitious and original developments along three main lines: i) Presteady state studies of NHE-1 microscopic kinetics using solid state support electrophysiology (funded by BQR University), ii) Role of NHE-1 in CD95 death receptor signaling, in particular explore which of the NHE-1 domains are required for the apoptotic effect of CD95 (InCA funded 2010-2013), and iii) Characterization of NHEs of intracellular organelles. This domain of cellular physiology is largely unknown but has far-reaching implications in cell and organ biology as well as in human diseases and ageing.

The feasibility of this project is assessed by past achievements and the excellent collaborative network of the team providing the necessary complementary expertise. While the mandatory biophysical studies of NHE-1 should be published in excellent, but perhaps lower impact journals, studies of NHE-1-CD95 crosstalk and of intracellular NHEs are likely to result in several publications in high profile journals.

- Conclusion :

  – Summary

Altogether, this is an excellent team that proposes an ambitious, original, and yet feasible project likely to result in an outstanding scientific output with a high potential for translational research.

  – Strengths and opportunities

Major strengths of the team are its highly regarded expertise in the field of proton transport/pH regulation, its pioneering work on NHE-1 involvement in cell division/death, as well as an excellent collaborative network and good financial support.

  – Weaknesses and threats

A weakness is its small size, which is likely to be at least partly overcome.

  – Recommendations

Funding is currently available for postdoc recruitment, with a high probability of obtaining further public and industrial support as the project and its applications develop. Along this line, it is mandatory that the full-time researcher of the team rapidly obtains a "Habilitation à Diriger les Recherches" to allow more PhD students in the team.

4.4.Team 4 : Integrative biology of epithelial transporters

Team Leader : Mr Christophe Duranton

- Staff members

	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)	0	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	?	?
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)		
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	

- Appreciation on the results

The main achievements of the team concerned studies on renal physiology and are related to effects of cadmium on one hand, and, on the other hand, the roles of CFTR and Task-2 in the regulation of cell volume and apoptosis. The results 21 articles since 2006) were published in very good journals respected by physiologist community (AJP, JBC, Free Rad Biol Med, Plos One…).

The data obtained have important translational extensions. This includes the use of CFTR inhibitor to protect the kidney during chemotherapy by cisplatin, and of the inhibitors of eIF5A hypusination to enhance hypoxic tolerance.

The strength of the team is its competences in physiology, and very good knowledge of approaches necessary to investigate the proposed projects. The team will be led by a young researcher following the recommendations of the previous AERES committee (2009). He has the maturity to lead the team. He will benefit of support of an experienced excellent researcher who has initiated many of the projects, which will be continued during next years. These projects led to patents applications. This senior researcher, still a member of the team, will now focus on translational studies with different clinical centers and industrial partners.

- 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 an excellent visibility. It has been attractive to students and has international, national and local partners. The team leader has organized 2 international meetings on Ion channels and became a president of 21st International Ion Chanel Congress in 2010. He was an invited speaker at University of Muenster.

One of the team members obtained the “Médaille de Bronze CNRS” award and was a finalist of Excelencia 2008 as an “Ingénieur en Centre de Recherche”.

The collaborations with excellent groups in Switzerland, Japan, Germany, USA, Mexico underlie the international visibility of the team and attest its participation to international network.

The team has had very good attractiveness for master and PhD students (3 phD thesis and 5 masters since 2006) but needs to improve the recruitments of post-docs. The team is able to raise funds, and organize pre-clinical studies.

Two strains of original transgenic mice engineered by the team were given to EMMA and 60 labs over the world utilize these strains.

The team has developed an industrial partnership (in collaboration with VALORPACA) concerning a new protective protocol against the renal failure induced by the antineoplastic drug cisplatin.

The Unit director identifies the projects of this team as those with the most important transfer potential. Several patents are in process with the University partner Valorpaca that is in charge of the applications. Valorpaca is also in the process of very actively contacting potential industrial partner in France.

The research was supported by grants form ANR (200 k€) and from Vaincre la Mucoviscidose (20 k€)

Two other patents are under analysis

- ## Appreciation on the scientific strategy and the project

The previous achievements of the team leader and of the senior scientist of the team provide guarantees that the proposed project will be realized. The projects are supported by ANR grants, and new applications are under evaluation. The project covers areas from basic science to clinics and industry. It is translational and could have potentially a high impact. The team possesses a solid expertise in the evaluation of the functional parameters of the renal function. Combining in vivo experiments, involving surgical operations, functional analysis and microanalysis, with in vitro models, exploring the molecular mechanisms of the adaptive and protective mechanisms observed in the in vivo models, is a strength of this project.

- ## Conclusion :

– Summary

The team has delinated 3 clear projects in the field of renal physiology, all with potential clinical and/or industrial extensions: i) Hypoxic tolerance and eIF5A hypusination; ii) Adaptive response to hypoxia : CFTR-HIF-ROS relationship; iii) Protection of renal function during cisplatin treatment: Role of CFTR

The team has all the necessary competences to realize these projects.

– Strengths and opportunities

The strength of the projects is the competence of the team in renal physiology in general, and in the experimental approaches. The existence of mice core facility as well as imaging core facility on the campus is an important plus. The competence and enthousiasm of the young leader who has full support of an experienced senior researcher is worth to be mentioned. The involvement in the educational activity of the University guarantees the recruitement of PhD students.

– Weaknesses and threats

A lack of man power, especially post-docs.

– Recommendations

Increase the number of grant applications would benefit the project. Try to hire a postdoc.

4.4.Team 5 : Bone marrow microenvironment and physiopathology of the inflammatory response

Team Leader: Ms Claudine Blin-Wakkach

- Staff members

	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)	0	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	0	0
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	0	
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	2	2

- Appreciation on the results

This team results from the fusion of two groups.

The first group studied the interactions between immune cells and osteoclasts, as well as more general questions in immunology (monocyte and regulatory T cell functions). It has obtained original results and has published 10 articles during the 2006-2010 period, including reports in good/excellent specialty journals such as J Immunol (x 2) and Blood. This group is recognized for its contributions in osteo-immunology, and made an important contribution showing the ability of osteoclasts to derive from dendritic cells, with functional properties (pro-inflammatory) quite different from those (anti-inflammatory) of conventional osteoclasts derived from monocytes/macrophages. It should be noted that osteo-immunology is an interesting field, with relatively few competition, even at the international level. This young group thus fills a “niche” in which it can provide original results in the international competition.

The second group is actually represented by a single scientist who comes from a larger team. He has been involved in a very competitive field, the differentiation of stem cells, and he succeeded to obtain original observations on stem cell differentiation towards neuroectodermal tissues and in the molecular events involved in stem cell differentiation, leading from 2006 to 2010 to seven publications in good specialty journals (including Cell Death Differ, Plos One, as well as significant contributions to J Cell Physiol and Stem cells, and a patent application). The personal involvement of this scientist in the scientific production of his former team is unquestionable. This scientist is not formally allowed to train students (no HDR), but contributed significantly to support two PhD students who both appeared as first author in a good publication (CDD and PlosOne, respectively), with an additional good publication in revision for the second student.

The originality of these partners is in their diverse expertise, combining immunology, mesenchymal stem cells and bone physiology, thus covering the most important cells involved in bone physiology. Although these two groups did not publish yet together, their knowledge are quite complementary. Recent and yet unpublished findings best illustrate the potential of this team, with quite interesting and innovative observations on the mechanisms of bone resorption during inflammatory diseases, involving osteoclast activation by activated cells from a specific subpopulation of T lymphocytes. Mesenchymal stem cells appear to play a role in this process, and the expertise of the scientist joining the first group is thus acknowledged.

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

The first group is repeatedly invited for national and European meetings on bone physiology, and the scientist of the second group participated in several meetings of the European network on stem cells (Epistem) to which it belonged.

These projects are supported by several different grants and are well funded.

The two members of the first group are allowed to train PhD students (HDR). This group trained so far a single PhD student up to the delivery of the thesis. This student appeared as second author in a 2008 publication (Blood) and as the first author in a manuscript in revision. Two additional PhD theses are ongoing.

Altogether, these two groups appear as relatively young scientists, with a good scientific production, and a good potential to improve their visibility in the next few years. This will be required for attraction of post-docs.

- Appreciation on the scientific strategy and the project

The project is in line with previous work evaluating the relationships between immune cells, mesenchymal stem cells and osteoclasts. These interactions are dual, with immune cells and mesenchymal cells influencing osteoclast, and vice versa. One of the leading hypothesis is that resident osteoclast should promote immune tolerance whereas osteoclasts associated with inflammation should in turn exacerbate further activation of immune cells. Such an opposite behavior of specific cell subpopulations is largely studied in immunology. The originality of this team is to extend this consideration to osteoclasts, a neglected cell population despite the critical role of the bone marrow as a reservoir of immune cells, and the consequences of osteoclast physiology on bone metabolism. The clinical relevance of the project is highlighted by the frequency of bone demineralization in inflammatory processes, either diffuse or localized.

There are interesting potential interactions with several other teams of the laboratory. This team brings its expertise on bone physiology, and this should benefit to several other projects of the laboratory, such as myoblast/osteoblast differentiation (team 2), NHE-1 (team 3) and CFTR (team 4) functions. Interactions between team 5 and others from the laboratory need to be further considered to lead to formal partnerships.

- Conclusion :

  - Summary

The overall feasibility of the project appears very good, as it extends previous studies of this group on osteo-immunology. This team is developing an interesting and original project on the interactions between osteoclasts and immune cells, a theme which warrants more attention from the scientific community than it received so far, and for which this relatively small team is in a good position in the international competition, considering its unique expertise at the cross road between bone metabolism, immunology and mesenchymal stem cells.

  - Strengths and opportunities

This field is specific enough to allow this group to produce original findings, as achieved so far.

The input of the scientist joining the group should still improve the competitiveness of the team.

The proximity of teams with different scientific background may result in novel and original approach for the project proposed.

  - Weaknesses and threats

This team may be too isolated, missing strong interactions with partners in their immediate vicinity involved in immunology or bone metabolism. Possibly, such partners are missing in Nice. Because the size of the team is relatively small, this may be a threat for the long term.

– Recommendations

On the long term, this team may suffer from its lack of partnerships with other local groups involved in immunology or bone metabolism. To avoid this threat, this team should develop as much as possible scientific collaborations and exchanges with partners within the new laboratory, as well as enlarge national or international networks. Beyond this central project of this team, there are potential and interesting interactions with other teams from the laboratory, which need to be explored.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
LABORATOIRE DE PHYSIOMÉDECINE MOLÉCULAIRE (LP2M)	**A**	**A**	**A+**	**A**	**A**
ION CHANNEL GENETICS [BARHANIN-BARHANIN]	A+	A+	Non noté	A	A+
ION CHANNELS IN NERVOUS, MUSCULAR AND CARDIAC DISORDERS [BARHANIN-BENDAHHOU]	A	B	Non noté	B	A
BONE MARROW MICROENVIRONMENT AND PHYSIOPATHOLOGY OF THE INFLAMMATORY RESPONSE [BARHANIN-BLIN-WAKKACH]	A	A	Non noté	A	A
PROTON DYNAMICS IN CELLULAR AND INTRACELLULAR COMPARTMENTS [BARHANIN-COUNILLON]	A	A	Non noté	A	A
INTEGRATIVE BIOLOGY OF EPITHELIAL TRANSPORTERS [BARHANIN-DURANTON]	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 11 avril 2011

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Ref : Rapport d'évaluation 2UR120001727 - Laboratoire de Physiomédecine Moléculaire (LP2M) - 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 « Laboratoire de Physiomédecine Moléculaire (LP2M) » portée par l'Université Nice Sophia Antipolis, vous voudrez bien trouver ci-joint la réponse que nous désirons apporter à ce rapport.

Celle-ci comporte à la fois quelques éléments correctifs factuels et des observations de portée générale visant à apporter notamment des précisions sur l'équipe n°2 de cette unité au regard des recommandations, par ailleurs considérées comme très positives, faites par le Comité de visite que nous remercions pour son travail constructif.

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

UNIVERSITE DE NICE - SOPHIA ANTIPOLIS
1.1.1996

Pour le Président de l'Université de
Nice-Sophia Antipolis et par délégation,
Le 1er Vice-Président

Pierre COULLET

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CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE

Jacques Barhanin
Directeur de Recherche au CNRS

Laurent Counillon
Professeur à l'UNS

Comments concerning the AERES report for the LP2M Laboratory

We thank the committee for the very careful evaluation of our laboratory and projects. We agree with the great majority of the points, and suggestions of the report, but would like to raise a few comments for team 2 led by our colleague Saïd Bendahhou. These are listed below :

Team 2 : Ion channels in nervous, muscular and cardiac disorders
Team Leader : Mr Said BENDAHHOU

A- We would like to address four main comments from the AERES report:

1-The topics of the team that are reported to be too narrow
2- The Scientific visibility and production reported to be too modest
3- The low attractivness
4- The complete dependence on clinical groups that are not in the neighborhood

B- Answers

1- Committee statement *"topic of the team is narrow"*

The main topic of the team is not restricted to Andersen's syndrome as stated in the committee summary but rather addresses issues that take into account all channelopathies.

In our team Kir2.1 and Andersen's syndrome are used as a model because they are involved in muscle and heart at the same time making them good tools for answering questions not only related to Andersen's syndrome pathology but also related to a larger spectrum of excitability disorders such as periodic paralysis, myotonia, LQT, and atrial fibrillation. In fact our last publication involved Nav1.4 and myotonia (*Simkin D., Léna I., Landrieu P., Lion-François L., Sternberg D., Fontaine B., and Bendahhou S. (2011) Mechanisms underlying a life-threatening skeletal muscle Na+ channel disorder. J. Physiol. (Lond.): accepted*).

2- The committee has stated *"best work dates to before 2008"*

The team's work has been published in highly ranked journals before and after 2008 (Am J Physiol (2009), PNAS (2010), JBC (2010), J Physiol (2011)). In addition, the h factor of the team leader (20) is well in the average of

the h factor of the team leaders in Life Sciences in Nice and cannot be regarded as a weakness as stated by the committee.

Concerning the publications of the Associate professor (MCU) of the team, that was stated to be too weak since 2008, it must be noticed that she has an HDR, has published 5 papers during years 2007 and 2008, an impressive accomplishment for even a fulltime researcher. The committee should also take into account that she had to switch from her previous topics of animal behavior and neurobiology when joining team 2 to focus on ion channel electrophysiological characterization in mammalian cells. She has since published an additional publication with our team showing her ability to adjust to a novel scientific environment (*J. Physiol 2011, see above*).

3- The committee did not take into account the good and active collaborative network that the team has built either at the local, national or international level. Even though this team was created only in 2009, it has already attracted:

- a PhD student from abroad (Rosalind Franklin University of Medicine and Science, USA) who was funded through national and international fellowships,
- an assistant professor (see above),
- a guest scientist: even more surprisingly, the report has also stated "no guest scientist was attracted", while Dr Uwe Fass (a visitor scientist, from November 2010) was part of the team and present during the committee visit.

4- The committee has stated *"The complete dependence on clinical groups not in the neighborhood of their institute is a threat".*

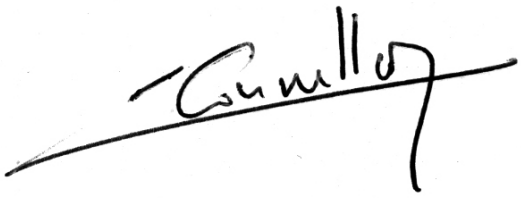
The two parts of this comment are in fact not correct :
Firstly, the aspects of the projects that involve biopsy recovery in humans have successfully achieved in collaboration with a local clinical group at the CHU of Nice (Pasteur Hospital), which is 10-min walking distance from our laboratory. We have also developed another collaboration with an international clinical network (Résocanaux) located at the Salpêtrière hospital in Paris, which is close in the national environment. This will allow the team to retrieve additional samples if needed.

Secondly, the team's topics are ***not completely*** relying on clinical groups. We have developed molecular tools to address physiological issues that do not involve human tissue. As noticed by the committee, we are using mammalian cell line for channel characterization and mouse models to address the involvement of the Kir2.1 channel in excitation-contraction process.

Taken together these two aspects are, in our opinion, strengths rather than threats.

Jacques Barhanin

Laurent Counillon



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