Transport ionique : aspects normaux et pathologiques

Rapport Hcéres

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

Section des Unités de recherche

Evaluation report

Research unit :

FRE 3093

University of Nice

March 2009

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Le Président de l'AERES	Section des unités de recherche
	Le Directeur
Jean-François Dhainaut	**Pierre Glorieux**

mars 2009

Evaluation report

The research unit :

Name of the research unit : FRE-3093

Requested label : UMR CNRS

N° in case of renewal :

Head of the research unit : Mr. Laurent COUNILLON

University or school :

Université de Nice Sophia Antipolis

Other institutions and research organization:

CNRS

Date(s) of the visit :

December 9th 2008

Members of the visiting committee

Chairman of the commitee :

Mrs. Bénédicte DARGENT, University of Aix-Marseille 2

Other committee members :

Mr Steven BROWN, University of Zurich, Switzerland

Mr Frédéric BOUILLAUD, Hôpital Necker Paris

Mr Jean-Louis BANERES, University of Montpellier 1&2

Mr Hervé ENSLEN, INSERM Paris

Mr Carsten WAGNER, University of Zurich, Switzerland

Mrs Michèle SILHOL, University of Montpellier 2

CNU, CoNRS, CSS INSERM, représentant INRA, INRIA, IRD.....) representatives :

Mrs Isabelle BARO , CoNRS representative

Observers

AERES scientific representative :

Mr Thierry RABILLOUD

University or school representative :

Mr LARDEAUX, University of Nice Sophia Antipolis

Research organization representative (s) :

Mr André LE BIVIC, Directeur Scientifique Adjoint, CNRS

1 • Short presentation of the research unit

- Numbers of lab members : 18
  - 3 researchers with teaching duties
  - 7 full time researchers
  - 5 HDR
  - 6 engineers, technicians and administrative assistants

7 PhD students who have obtained their PhD during the last four years

2 PhD students currently present in the research unit

Numbers of "publishing" lab members (among permanent researchers with or without teaching duties): 10

2 • Preparation and execution of the visit

Overview presentation by the director was done in the presence of committee members in the meeting room of FRE-3093. It was followed by the presentations of the team projects done by team leaders (15 min presentation, 5 min questions). Then, the committee visited the laboratory to check the working conditions. During the lunch and the coffee breaks, all team members including students and post-docs were present for informal discussions with committee members depending on their interests.

Before the final private meeting of the committee for preparation of the report, the committee members organized into two subgroups. One subgroup had an informal discussion with the permanent staff, including scientific, technical and administrative personnel; the other one with the students and the post-docs.

3 • Overall appreciation of the activity of the research unit, of its links with local, national and international partners

Preliminary comments

Two previous laboratories merged in 2005. The unprepared situation was a fiasco. The CNRS decided to split the teams in two different "formation de Recherche en évolution " : FRE-3093 and FRE-3094.

FRE-3093 was created in January 2008 for two years. It is located in a 40 year old building in the Valrose Park of the Nice University. The space allocated to FRE- 3093 has been renovated.

FRE-3093 is composed of 3 teams sharing common scientific interests on ion channels and transporters. One of the teams joined FRE-3093 in early 2008. The teams are heterogeneous in term of human resources. The level of publications is also heterogeneous ranging from excellent to good-medium. During his presentation, the director underlined the decision of the teams to keep students number to a minimum "to give priority to quality of training instead of quantity before the situation is clarified over a long enough period"

FRE-3093 applies for the creation of a novel research unit "Unité Mixte de Recherche" (UMR).

4 •Specific appreciation team by team and/or project by project

TEAM 1. "Genetic of ion channels"

The team includes its leader, a CNRS senior research scientist (DR1), a CNRS research scientist (CR1), An assistant professor (MCU), an half time technician and a PhD student co-supervised with Chicago University.

Past Research

This group is well-recognized in the field of ion channels with a high visibility on the international scene. In 2008, this team left the IPMC, an institute with high quality working surroundings both at the scientific and infrastructures levels, to join FRE-3093. The group has a dense and fruitful network of collaborations in its former laboratory as well as with others laboratories at the national and international plans. The team leader has signed since 2004 18 papers in international peer –reviewed journals, with several papers in very good to excellent journals (e.g. Cell, PNAS, EMBO J., Huma. Mol. Genet J. Biol. Chem,.), including 3 papers in collaboration with Team 3. Team 1 has one patent issued and another one deposited. The CR1 researcher has written two book chapters in press at the time of the visit.

The past scientific activity was oriented towards 3 axes. First, Team 1 functionally characterized different ion channels involved in cardiac and muscular familial diseases. Team 1 discovered the ion channel molecular complex KCNQ1-KCNE1, which is associated with the cardiac long QT syndrome when mutated. It also showed its implication in familial atrial fibrillation. More recently, they characterized mutants of Kir2.1 responsible for the syndrome of Andersen, a pathology of skeletal and cardiac muscles and bone development. Team 1 has started to develop a network with clinicians in order to study Kir2.1 mutants from patient muscle biopsies. Team 1 also contributed to the studies of other cardiac K^+ channels involved in various cardiac familial diseases.

Second, this group has developed a genetic approach (conditional KO) to obtain novel insights into the physiological roles of the TASK 1-3 potassium channels. Its main contributions include the demonstration of the role of TASK channels in adrenal gland zonation and mineralocorticoid homeostasis and in the respiratory control.

Finally, in collaboration with two teams of its former lab, they proved that that sumoylation does not regulate surface expression of TWICK1 channels, unlike previously published.

Future Directions

Over the next few years, the team leader proposes to continue two independent projects. The first one deals with the physiopathology of the Andersen syndrome. Team 1 proposes to pursue the functional characterization of Kir2.1 channels in normal situation and in Andersen syndrome, in attempts to uncover the role of Kir2.1 potassium channels in excitation-contraction. The impact of Andersen syndrome mutations on Kir2.1 function and localization will be evaluated in vivo after viral trasfection. The second project aims at deciphering the role of TASK channels in the control of adrenal gland zonation and mineralocorticoid homeostasis and in the respiratory control by combining a large spectra of multiple and complementary approaches. Achievements of the proposed projects require a dense network of already established collaborations but these appear to be already established. One of the two projects will be headed in a near future by the CR1 researcher of the team.

Fundings

The team has obtained ANR (2008) and international (PICS) fundings as well as grants from charity organization (AFM) and from the region Provence Alples Cote d'Azur.

Conclusions

The project is structured on solid basis. Given the multi-faceted role of task channels in several aspects of physiology, the group should make fruitful scientific contributions to multiple research programs. A minor issue concerns the present facilities and working environment that may impact the kinetic of the exploitation of the projects. However, given the stage of the projects and the well-driven network of collaborations, at the national and international plans, the committee is confident that this team will maintain its high level of scientific production in the future. The laboratory should largely benefit from the expertise and the dynamism of this new team.

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A+	A+	A+	A	A+

Team 2 -"Molecular mechanisms of pH regulation"

The team regroups 1 Professor, 1 CNRS research scientist (CR2) recently recruited and 1 technician. The projects of the team focus on regulation of intracellular pH (pH_i) by the Na^+/H^+ exchanger (NHE-1) in health and diseases.

Quality of the past research

NHE-1, expressed in virtually all tissues extrudes protons under conditions of intracellular acidosis. The team leader signed 5 papers since 2004, in peer-reviewed international journals of medium to good quality. In an EMBO report, the team exposed a new concept regarding the mechanism governing the NHE1 regulation by pH_i. More recently, the team, associated with a laboratory in Rennes, deciphered the regulation mechanisms by osmotic changes (1 Biochemistry, as PI) and by lipids of the membrane (1 J Cell Physiol as co-PI). On a more preclinical aspect, the team researches concern also the role of NHE-1 in cancer and heart failure. As collaborator of the same lab, the team studied the NHE-1 involvement in the effects of cisplatine, used in cancer chemotherapy, on cell death, revealing a potentially new therapeutic target in cancer (1 Cancer Res). In collaboration with another local laboratory, the team also studied the involvement of AMPK signaling pathway in the exchanger regulation that may explain its cardio-protective effects (1 Endocrinology as collaborator).

Future plans

Over the next years the team proposes to pursue its projects. The structure-function, pharmacology and molecular regulation of NHE-1 will be further investigated. Despite the collaboration with local biophysicists, the project regarding mathematical modeling of pH_i regulation may appear too ambitious in regard to the small size of the team. The CR2 scientist will conduct investigations on the characterization of CIC Cl^- channels and NHE-6 exchanger of intracellular compartments. This project, in continuation with the scientist's post-doc work is concentrated on regulation of the various molecular actors. The aspects regarding their role in molecular regulation of intracellular compartment pH will be to further investigate. The team needs to be reinforced in order to develop more ambitious projects. Part of these projects will be conducted in collaboration with other French and European laboratories. No financial support is mentioned.

Conclusion

The research carried out by this team is interesting and certainly of relevance in the medical field. It has contributed in the past to pH regulation research with key works. Considering the teaching and management activities of the group leader, the recruitment of a junior staff member should be considered in the future to strengthen this small team.

MÉCANISMES MOLÉCULAIRES DE LA RÉGULATION DU PH

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
B	B	B	A	B

TEAM 3. "Integrative biology of epithelial channels and transporters"

The team consists of 4 scientists with permanent CNRS positions (one DR1, one DR2 and two CR1), one assistant professor (MCU), one permanent CNRS engineer and one PhD student. Scientifically, the focus of the group has been studying renal ion transport and ion channels using transgenic animals and cell culture models.

Quality of the past research

In the past years the group has published 16 papers since 2004, in peer-reviewed international journals of medium to good quality. The current leader of the group has had only 2 senior authorships in this period, whereas the former group leader signed as last author most of the other papers. Of note, in the report for this evaluation many publications are listed that originated from work of members of this group while performing their postdoctoral training elsewhere. Team 3 has 1 patent deposited. The negotiation of one license with the Lexicon Company is also in progress for the use of transgenic mice. Two lines of transgenic mice established in team 3, have been accepted at the EMMA. They have been distributed to numerous laboratories in different countries.

Future plans

The group proposes to focus their future research mainly in the field of the CFTR channel in apoptosis and redox stress as well as to study renal effects of cadmium. The integration of these activities with the research of the others groups remains vague. The apparent lack of visions and projects on the scientific fore-front appeared as an important issue to the committee. Moreover, the group has a major problem in supporting and promoting young scientists on their way into independence.

Fundings

Financial support is provided by part of the collaborative ANR grant (ANR genopath 2008) and by one grant from charity organization.

Conclusion

In conclusion, team 3 appears to have no major vision for their future research. The integration with the other two groups is not obvious despite sharing the common interest in membrane transport proteins. During the visit, the committee unanimously felt that the former head of Team 3 was still overshadowing and running the group.

BIOLOGIE INTÉGRATIVE DES CANAUX ET TRANSPORTEURS ÉPITHÉLIAUX

Note de l'équipe	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
B	B	B	C	C

5 • Appreciation of resources and of the life of the research unit

Although, the 3 teams share common interests on the study of ion channels and membrane transporters, the dynamic interactions and synergy between them were not apparent during the visit, despite a genuine willingness of each group leader. The committee felt that the management of the laboratory lacks of common and osmotic driving force. The transitory structure of the laboratory impacts the recruitment of new PhD students and of postdoc fellows. The committee noted the weak scientific emancipation of the CR1 members.

6 • Recommendations and advice

— **Strong points :**

FRE-3093 attracted an excellent team. This constitutes a strong driving force for the emergence of a new laboratory.

— **What needs to be improved :**

CR1 researchers should be encouraged to obtain HDR and most importantly to affirm their scientific personalities.

Despite the presence of a well-recognized team, the international visibility of the laboratory needs to be reinforced.

The committee felt that the FRE-3093 may not have the critical scientific mass and the core funding required for a self-standing laboratory.

— **Recommendations :**

Together with an adequate management of the human resources, the integration of Team 1 should provide the catalyst necessary for a new start. The committee invites the group leader of Team 1 to deeply commit himself in the scientific and human life of the unit.

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Note de l'unité	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
B	A	B	C	B