Biologie et physiopathologie des systèmes intégrés

Rapport Hcéres

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

Section des Unités de recherche

Evaluation report

Research unit :

FRE 3094

University of Nice

March 2009

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

Section des Unités de recherche

Evaluation report

Research unit :

FRE 3094

University of Nice

Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

mars 2009

Evaluation report

The research unit :

Name of the research unit : FRE-3094

Requested label :

N° in case of renewal :

Head of the research unit : Mr. Franck DELAUNAY

University or school :

University of Nice Sophia Antipolis

Other institutions and research organization:

CNRS

Date(s) of the visit :

December 8th 2008

Members of the visiting committee

Chairman of the commitee :

Mrs. Bénédicte DARGENT, University of Aix-Marseille 2

Other committee members :

Mrs Isabelle BARO , University of Nantes

Mr Steven BROWN, University of Zurich, Switzerland

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

Mr Hervé ENSLEN, INSERM Paris

Mr Carsten WAGNER, University of Zurich, Switzerland

Mrs Michèle SILHOL, University of Montpellier II

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

Mr Frédéric BOUILLAUD, 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 : 27
  - 6 researchers with teaching duties
  - 10 full time researchers
  - 9 HDR
  - 7 engineers, technicians and administrative assistants (2 will retire in 2009)

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

1 PhD student currently present in the research unit

3 postdoctoral fellows currently present in the resarch unit

Number of "publishing" lab members (among permanent researchers with or without teaching duties): 14/16

2 • Preparation and execution of the visit

Overview presentation by the director was done in the presence of committee members in the castle of the Valrose park. It was followed by the presentations of the team project done by team leaders (15 min presentation, 5 min questions). 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. Then, the committee members were 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. Before the final private meeting of the committee for preparation of the report, the committee visited the laboratory to check the working conditions.

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

Preliminary comments

The 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-3094 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- 3094 was timeworn and located on two different levels. One level has been renovated, the other one is undergoing renovation.

FRE-3094 is composed of 5 heterogeneous teams, both in terms of research topics and human ressources. During the visit and the presentation of the team leaders, the committee unamimously felt that previous events led to an incredibly difficult working environment until 2008. These conditions clearly impacted the ability of the different teams to recruit new PhD students and researchers since 2005.

Despite these facts, and in the context of (again) a transitory structure, the committee has found that overall FRE-3094 teams have been highly motivated, focusing their energy on realistic and reachable work objectives.

FRE-3094 does not apply for a creation of a novel research unit. FRE-3094 members plan to integrate either as teams or as individual scientists in existing laboratories from the University of Nice, depending on scientific and human factors. 3 Teams have already made precise plans to join the neighbooring "Institut de Biologie du Développement et Cancer (IBDC/UMR CNRS 6543).

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

TEAM 1. Peripheral Clocks and the Circadian System

This team is comprised of seven members: its leader (PU1), two university researchers (MCU, University of Nice), one CNRS researcher (CR1), two postdoctoral fellows and a technician.

Past Research

This young group has succeeded in establishing itself firmly on the international scene via innovative research into the physiological roles of the mammalian circadian clock that governs diurnal behavior. It has carved a niche for itself by exploring in particular the roles of peripheral clocks, cell-autonomous daily timekeepers present in most cells of the body. Its main contributions include the discovery of a molecular mechanism by which this clock governs the cell cycle; and secondly, the discovery of a circadian transcription factor (KLF10) that plays a crucial role in governing metabolism. This research has been published in ten papers in international journals, of good to very good rank (e.g. Mol Cell Biol, J Biol Chem)

Future Directions

This team will be integrated as an independent team into the neighboring IBDC Institute. The facilities and working environment that the integration provides should be the catalyst necessary to allow its members to exploit the full potential of their projects. These include not only continuing to explore the role of KLF10 and the PPAR family of nuclear receptors whose molecular targets it shares, but also functional studies to analyze the role of the circadian clock during cancer cell proliferation.

Funding

The team has played a role in two EU Framework 6 projects, TEMPO and Crescendo. At the time of evaluation, two postdoctoral fellows were supported by extramural funding. This further shows the insertion of the lab in the European networks of the field

Conclusions

With a good near-term pipeline and innovative ideas for the more distant future, the group should be poised to continue its development. Given the multi-faceted role that the circadian clock plays in many aspects of physiology, the group should also be able to make fruitful scientific contributions to multiple research programs within the unit that it plans to join.

HORLOGES PÉRIPHÉRIQUES ET RYTHME CIRCADIEN

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 2. Ionic transports and associated pathologies

The team leader is a CNRS senior research scientist (DR2). Team 2 includes 1 Professor, 3 CNRS research scientists (CR1), and 1 Assistant Professor (MCU). The projects of the team focus on the Cl^-/HCO_3^- exchangers (AE family) and ion channels in health and diseases.

Quality of the past research

The team leader associated with a CR1 conducted projects on AE1, highly expressed in erythrocytes and kidney. Despite a high homology, human AE1(hAE1) is responsible for CO_2 transport only whereas, in fish erythrocytes, it is also in charge of cell volume regulation and is an anion channel also permeable to various organic solutes. Team 2 characterized the pore and transporter regions structure of the trout protein (tAE1). It also contributed to the

discovery that, when the hAE1 is mutated (erythrocytes or kidney diseases), the channel activity reappears and originates the red cell high permeability to ions.

The other senior scientist focused on characterization of epithelial Cl^- channels, alternative to CFTR, in the context of cystic fibrosis. These proteins are potential targets to restore some epithelial Cl^- flux impaired in this disease.

A third axis is dedicated to the study of the ion channels in the context of cancer, subject of a recent and growing interest in this field. The Assistant Professor leading this project focused on a so-called orphan receptor used as cancer biomarker: the σ1-receptor. He is one of the few persons in the world dedicated to the study of the function of this protein. He showed that σ1-receptor regulates ion conductance and that its ligands can potentially be used to control tumor cells growth.

These past research has led to 16 publications in international peer –reviewed journals, with several papers in very good international journals of the field (e.g. Blood, J. Biol. Chem, J Cell Physiol). However, invited conferences are rather scarce

Future plans

Team 2 plans to join IBDC/UMR CNRS 6543. It proposes to pursue two principal axes. The first axis aims at determining the structure/function of hAE1 and its implication in diseases where the erythrocyte permeability is increased. The original hypothesis that mutations or parasite infection (i.e. malaria) modify the equilibrium between 2 conformations (electroneutral transport *vs* anion channel) of the hAE1will be evaluated.

Second axis aims at analyzing the σ1-receptor functions in the mitochondial membrane to understand how the protein may prevent apoptosis. Finally, its role in the regulation of the K^+ channel HERG, highly expressed in aggressive myeloid leukemia cells, and of the integrin pathway will be investigated in order to understand its involvement in the cancer severity and to limit it.

The senior scientist involved in the study of epithelial Cl^- channels will retire very soon (December 2009). Meanwhile, he will continue to investigate alternative Cl- conductances of the bronchial epithelium focusing on SLC26A9 and Bestrophin 3 and 4.

Funding

The team should have some concerns about the long term-viability since the fundings are presently grants from charity organizations only.

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 epithelium physiology research with interesting works. The role the CR1 researchers in the projects should be clarified and their autonomy favored by passing the "HDR" if not already done. The main concern regards the poor level of personal funding that will allow planning post-doc and student recruitment.

TRANSPORTS IONIQUES ET PATHOLOGIES ASSOCIÉES

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	B	B

Team 3. Expression, purification and structural analysis of membrane proteins involved in pathologies"

Structural information on G protein-coupled receptors (GPCRs) is sparse due to the difficulties in producing large amounts of functional protein and in stabilizing the protein native fold out of a membrane environment. In this context, Team 3 works on the production and purification of membrane proteins for structural studies. This group is actually composed of two tenure researchers, the team leader (CR1 CNRS) and one CR1 (INSERM), a post-doctoral fellow and a PhD student.

Quality of the past research

This group has explored for the last four years common strategies for expressing and purifying proteins of the hedgehog pathway in yeast and drosophila cells. They also devised SPR-based techniques for monitoring receptor functionality after purification. A French patent has been recently deposited on these topics. Originality relies on the proteins selected, Patched and smoothened, but are far from being the simplest models for structural studies on GPCRs. The quality of publications of team 3 is ranked as a medium-good impact. The publication record of the group for the last two years is limited (only 3 papers, but all in international peer-reviewed journals), but promising results have been obtained that could open the way to crystallization in a near future. The group has been recently asked to organize a CNRS school and to edit a book on this topic, which shows its recognition in its scientific area.

Future plans

The proposed project is the logical continuation of current research on expression and purification of Patched and smoothened for crystallization purposes. They also plan to develop parallel functional studies for characterizing protein ligands and interacting partners. Team 3 also started the expression of a series of AE1 transporter mutants in collaboration with Team 2 and plan to work further along this line. Merging both groups in a near future, as proposed by both group leaders, is fully supported by the committee.

Funding

This program has been essentially funded for the last three years by a european network program (STREP FP6). This funding ends in 2009 but a funding from the Conseil Général des Alpes Maritimes has been awarded this year for equivalent amounts. They also benefited from smaller grants from non-profit agencies.

Conclusions

This group develops a risky program that should be encouraged. The limited number of staff scientists working on this topic should be relieved by tighter contacts with Team 2, as proposed by their respective group leaders.

EXPRESSION PURIFICATION ET ANALYSE STRUCTURALE DES PROTÉINES MEMBRANAIRE

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	B	Non noté

Team 4 . Signalling and muscle regeneration

The team leader has a strong background in cell signaling particularly signaling cascades involving protein kinases. This team is composed of two researchers with tenure positions, the team leader (CR1 CNRS) and an assistant Professor (MCU).

Quality of the past research

The research mainly focused on the regulation and the roles of the Akt and MAP kinases pathways in muscle. The team leader signed 7 papers since 2004, in peer-reviewed international journals of medium impact. On 2 thereof he figures as senior and corresponding author (2004 and 2006). Two manuscripts extending both studies were in preparation at the time of the visit. A new collaborative project with a laboratory from the Karolinska Institute (Sweden) has also been initiated aiming at identifying partners of Twinkle , a mitochondrial helicase that is essential for the maintenance and replication of mitochondrial DNA, particularly in muscle. A partner identified by two-hybrid screening has been further validated and its localization to mitochondria demonstrated. In addition to the publications, two US patents have been co-authored by the team leader, but they refer to research carried out before the 4-year plan of interest to the committee.

Future plans

Over the next few years, the team leader proposes to develop two independent projects. The first one is in line with his previous interest and is part of a larger collaborative study proposing to identify the signaling pathways involved in muscle wasting during aging of the obese individuals using *in vitro* and *in vivo* approaches. The present team will perform the *in vitro* studies. The second project is to pursue the collaborative study with the Swedish laboratory, one of the top laboratories in the field. The precise function of the interaction between Twinkle and its partner in mitochondria will be characterized using shRNA and in a long term prospect, by generating conditional knock-out mice of the Twinkle partner.

These projects were felt interesting, but the committee identified several issues. First, concerns were expressed with regards to productivity because of the limited publication record since 2006, although it may be due in part to the reduced size of the team over the past 2-3 years. Second (and consequently) the present size of the team is a major handicap to develop ambitious and productive projects. Finally, at the time of the visit, the team leader did not know which laboratory his team will join after 2009.

Funding

Financial support is only provided by part of the collaborative ANR grant related to the first project for the next 3 years.

Conclusions

The committee urged the team leader to submit his most recent work soon and to take action in identifying a laboratory for 2010. The recruitment of new team member and additional financial support also appear important to elaborate the proposed projects.

SIGNALISATION ET RÉGÉNÉRATION MUSCULAIRE

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

Team 5 .Transcriptional regulation and differentiation

The main interest of this group is the role of transcription factors in cellular proliferation, differentiation and apoptosis. However, to put its scientific activity in closer relationship with the department in which this group was inserted five years ago, it initiated new projects dealing for example with the toxicity of Cadmium.

Quality of past research

During the past years (2005-2008), this team has been studying :

- Cadmium toxicity : that led to the description of an unconventional activation of ERK.
- Bone differentiation : this was a joint project with a private company. Part of the results remain confidential other have been published.
- Technological issues : this team remains active in the process of developing tools or to improve existing ones. The activity deals with improvement of retroviral vectors or creation of software. These items were made available to the scientific community.
- Collaborations were running inside the department (recombinant expression of SLC26A9) and outside (Fragile X Mental retardation Protein; miRNA and cancer cell resistance to treatment). These collaborations rely on the expertise of the team in the use of retroviral vectors and IRES activity (control of translation by mRNA sequences).

With the small size of the group and such diverse research interests, the research of the group has led to 7 publications in peer-reviewed international journals of medium impact, but nothing else could be reasonably expected under such circumstances. However, the committee perceived positively the technological developments and their openness to the scientific community.

DIFFÉRENCIATION ET RÉGULATION TRANSCRIPTIONNELLE

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	B	Non noté

Future Plans funding and conclusion

While affected by the past events, the team leader and the person presently still working with him appeared realistic and still motivated to make meaningful science. As an example they proposed a short term project concerning Induced Pluripotent Cells (IPS) that would fit within the time and budget (raised by themselves) left before the reshaping of the department. The risk is high but if successful this project may have a major impact.

Team 5 was originally constituted by three scientists and one technician. Two persons are now retired, another will retire within three years. The present team leader is the only one who will remain. Although the scientific record of the team leader would appear fully consistent with the main interest of the IBDC center he is not supposed/appealed to do so. Consequently, he is currently searching for the possibility to integrate other laboratories interested in his expertise.

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

The director of FRE-3094 has created a rich and supportive environment for his team members and other members of the FRE-3094. Despite a difficult start, FRE-3094 members are overall still enthusiastic about moving to existing laboratories and about their challenging insertion into a highly competitive institute like IBDC. Moreover, it is clear that the difficult conditions for doing research (e.g. state of the building) have impacted much more strongly the smaller teams than the larger ones.

6 • Recommendations and advice

- **Strong points :**

Some teams (especially teams 1 and 2) have developed quite original research and have carved nice niches in their respective fields.

- **What needs to be improved :**

The number of PhD students and post-doctoral fellows per team should be improved.

CR1 reserachers should be encouraged to obtain HDR and to take over project responsabilities.

- **Recommendations :**

The committee has unanimously felt that Team 2 and Team 3 will mutually benefit to merge and strongly encourage them to take action as soon as possible.

The committe fully supported that the merge project of Team 1, Team 2 and Team 3 to IBDC. Undoubtebly, the facilities and the working environment that the integration shall provide, should allow them to exploit the full potential of their projects. The committee has appreciated that FRE 3094 members challenge insertion in IBDC institute.

The committee invites the university of Nice Sophia Antipolis and the CNRS life departement to help and assist Team 4 and Team 5 in identifying existing laboratories interested in their respective expertise and willing to welcome them for a "new start".

Biologie et physiopathologie des systèmes intégrés - FRE3094

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	B	B	B	Non noté