Signalisation et physiopathologie cardiaque

Rapport Hcéres

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

Section des Unités de recherche

Evaluation report

Research unit :

Signaling and Cardiac Pathophysiology

University Paris 11

January 2009

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Research unit

Signaling and Cardiac Pathophysiology

University Paris 11

Le Président
de l'AERES

Jean-François Dhainaut

Section des unités
de recherche

Le Directeur

Pierre Glorieux

january 2009

Evaluation report

The research unit :

Name of the research unit : Signaling and Cardiac Pathophysiology

Requested label : UMR_S INSERM

N° in case of renewal : UMR-S 769

Head of the research unit : M. Rodolphe FISCHMEISTER

University or school : Paris 11

Université Paris 11

Other institutions and research organization:

INSERM

CNRS

Date of the visit :

January, 13th 2009

Members of the visiting committee

Chairman of the commitee :

Mr Luc ROCHETTE, University of Dijon

Other committee members :

Mr Thierry PEDRAZZINI, University of Lausanne

Mr Dirk BRUTSAERT, University of Antwerp

Mrs Manuela ZACCOLO, University of Glasgow

Mr Xavier LEVERVE, University of Grenoble

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

Mr Michel OVIZE, CSS INSERM representative

AERES scientific representative:

Mr Bernard LEVY

University or school representatives:

Mr Didier SAMUEL, University of Paris 11

Mr Marc PALLARDY, University of Paris 11

Research organization representative:

M. Raymond BAZIN, INSERM

Evaluation report

1 • Short presentation of the research unit

- Total number of lab members: 32
  - Researchers with teaching duties: 5
  - Full time researchers: 7, including 4 Inserm and 3 CNRS
  - Engineers, technicians and administrative assistants : 7
  - PhD students: 10
  - Post-doctoral fellows: 3
- Numbers of students who have obtained their PhD since 4 years: 9
- Average length of a PhD during the past 4 years: 3.5 years
- Numbers of HDR: 8
- Numbers of lab members who have been granted a PEDR: 1
- Numbers of "publishing" lab members: 12 out of 12

2 • Preparation and execution of the visit

The site visit was perfectly organized, the commitee members obtained all requested informations and had the opportunity to get discussions with all reseachers, students, and technician staff.

The program is below:

Door-closed meeting: Committee members and AERES representative: 30 minutes

Door-closed meeting: Committee members, AERES representative and the Director: 15 minutes

Presentation of the unit: 30 minutes

Team 1: «Energetic Signaling and Cardiac and Muscular Pathophysiology»: 60 minutes

Team 2: «Cyclic Nucleotide Signaling and Cardiac and Vascular Pathophysiology»: 60 minutes

Team 3: « Small G Protein Signaling and Cardiac Pathophysiology»: 60 minutes

Lunch break in the laboratory with all lab members: 60 minutes

Three 30 minutes meetings:

Meeting with PhD students and postdoctoral fellows

Meeting with engineers, technicians and administrative assistants

Meeting with researchers with permanent position

Committee members, AERES representative, University and Research Organization representatives:30 m

Deliberation of the committee members and AERES representative: 60 minutes

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

This research unit was created on January 2006 and affiliated to the University Paris-Sud 11. It receives a budget from this University which employs several personals integrated to the Unit. The research unit is affiliated to Inserm (4 full-time researchers) and CNRS (3 full-time researchers). The unit 769 is also affiliated to the Federative Institute (IFR-141 – Institut d'Innovation Thérapeutique: du Fondamental au Médicament) ; this IFR has been directed during the last 4-year term by the head of the unit 769. It is important to note that important local collaborations have been established with chemists (seven common publications since 2003) and with another lab in the site (Unit 749, publication of a collaborative work in Nat Cell Biol 2003). An important point concerning this campus is the existence of technical platforms (imaging, transcriptomic, proteomic, animal center) associated with a highly qualified technical staff.

The scientific project is based on the study of signaling pathways in the cardiomyocyte and their specific alterations associated with the development of cardiac hypertrophy and heart failure. The general goal of the Unit is to better understand the molecular and cellular mechanisms by which the stimuli (physiologic and pathologic) act through the specific membranes receptors or ion channels and on intracellular compartments (sarcoplamic reticulum, mitochondria,..). The dynamic microcompartments are also studied. The identification of new therapeutic targets and molecules to improve myocardial function was explored. During the last years, it is important to note that the functional approach has been enlarged and that the collaboration with clinical teams has been initiated.

This Unit is includes three Teams:

- Team 1: Energetic signaling and cardiac and muscular pathophysiology
- Team 2: Cyclic nucleotide signaling and cardiac and vascular pathophysiology
- Team 3: Small G protein signaling and cardiac pathophysiology

Since 2003, 9 Students obtained a PhD (These d'Université) in this Unit, 3 in Team#1, 2 in Team#2, and 4 in Team#3. Between 1997 and 2008, 17 PhD Students were trained in the Laboratory, among them: 3 are now integrated in U 769. In return, it appears that U769 is not attractive to MDs and had limited capacities to recruit post-doc researchers.

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

Team 1: Energetic signaling and cardiac and muscular pathophysiology

During the last four years, the Team#1 investigated energetic signaling aiming to better understand the modulation of energy metabolism in the cardiac and skeletal muscle cells. The originality of its work is based on a subcellular approach, the interactions between microcompartments being investigated in an integrated physiological point of view. In particular the team has focused on the binding of creatine kinases to these compartments allowing a very efficient function. Based on their results, they propose that the origin of the metabolic failure of the failing heart is linked to an alteration of the mitochondrial biogenesis transcription cascade. The project of team#1 is in direct line with its previous results, aiming at understanding the energetic balance in heart failure (HF).

The team#1 proposes to study:

- how cardiomyocyte cyto-architecture, molecular composition and energetics determine contractile activity,
- the extracellular signals and signaling pathways involved in the energetic plasticity of cardiomyocytes and

- the myocardial energetic status in the heart and in the skeletal muscle. The researchers will consider simultaneously both physiological and pathophysiological aspects.

The scientific production resulting from this research activity is good in both quantitative (44 published papers between 2004 and 2008) and qualitative (most of the papers are published in the best rank of the discipline and some are in highly recognized journals) aspects. There is no doubt about the recognition of the quality of the work done by the team # 1 by the international community of researchers in this field. In particular their work on cellular channeling and compartmentation of energy fluxes in the cell as really be pioneering and recognized as such, especially for the aspect related to the pathophysiology of energy in the failing heart. The number and the quality of the meetings in which they are regularly invited as speakers support such assessment. The team has good national and international collaborations with several of the best world-leader teams in the field, however clinical collaboration appears to be rather weak. National and international research programs fund them.

The scientific project is very large and in line with the previous results, however, it is based on several hypotheses, which are so far not all yet verified. In this respect, the program is indeed innovative. The first part on mitochondrial biogenesis and energy signaling in health and disease is based on a causal relationship between the transcriptional coactivator peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) and its transcriptional control or regulation (calcineurin and Ca2+-calmodulin dependent kinase (CAMK), cAMP and cGMP, energy-dependent pathways (like the AMP dependent protein kinase, AMPK), hormones like thyroid hormone, cyclin-dependent kinases) and the deleterious events related to the energy deficit in the failing heart. This is indeed an attractive hypothesis, however the causality of this relationship and its deleterious rather than adaptive consequence remains to be shown.

The second objective aims to seek at new therapeutic targets based on the hypothesis that energy metabolism improvement after exercise training might be beneficial for cardiac, skeletal and vascular energy metabolism. Indeed understanding the mechanism allowing the beneficial effect of physical training might be attractive to elucidate new therapeutic targets and among them polyphenols and new pharmaceutical modulators of PGC-1α might be prioritized.

The third and last objective is to investigate the relationships between cell function, energetic and cytoarchitecture in healthy and failing heart mainly based on investigations of the mitochondrial dynamic. The tight connection between the organization of the mitochondrial network and the efficiency and integrity of mammalian adult cardiomyocyte is well established and the hypothesis that a disruption may precipitate energetic inefficiency and cardiac failure is very attractive.

Taken together the different aims of the scientific project are very ambitious and there might be some discrepancy between the size and the human resources and the scientific ambition of the group. The experimental facilities are present and the scientific background is sounding even if some hypothesis on which it based remain to be verified.

— Strong points:

- The research porject is based on a major public health problem : there are very large social implications and potential benefit for patients suffering from heart failure ;
- Very good recognition of the team in the field, good scientific production,
- Innovative hypotheses potentially leading to new therapeutic approaches ;
- Dynamic, enthusiastic and motivated team members;
- Very good platforms and experimental tools

— Weak points:

- Although some clinical collaborations have already been settled, the lack of cinical connection is a weakness
- The limitation of the human ressources is also a weakness for such a large project.

— Recommendations:

- The project appears to be too large considering the current number of researchers in the team, it should be probably resized and the major objectives better prioritized;
- Alternative hypothesis in case of some are not verified should be considered;
- Recrutement of senior scientists and post-docs should be seriously considered.

Nom de l'équipe : Energetic signaling and cardiac and muscular pathophysiology

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 : Cyclic nucleotide signaling and cardiac and vascular pathophysiology

The work of this team has been focused on understanding the intracellular organization of cyclic nucleotides pathways with a specific interest in the spatial organization and compartmentalization of the signalling events, and the changes occurring pathophysiological conditions, such as heart failure. The team uses an innovative approach based on the combination of electrophysiological and imaging techniques coupled to the analysis of functional parameters of the cardiac cell. The working hypothesis of the team is that compartmentalization of cyclic nucleotides is required for adequate targeting of the information generated at the membrane and that alteration of such compartmentalization is responsible for disease. The goal of the team is to understand the molecular mechanisms underlying such compartmentalization and to explore the possibility to restore compartmentalization as a therapeutic strategy.

Over the past four years the team has contributed to establish the concept of compartmentalized cyclic nucleotide signalling in the heart and to define the mechanisms underpinning such spatial control. They have defined the key role of phosphodiesterases (PDE) in the spatial control of cyclic nucleotide signalling. They have shown that a differential coupling between receptors and PDEs represents an important mechanism to generate heterogeneous cAMP signals to different hormones and found a down regulation of specific PDE isoforms in a rat model of cardiac hypertrophy. Studies the team has conducted in human tissue indicate a differential role for b3-AR in the atrium and in the ventriculum. The results of this research has led to publications on high impact journals and the team is internationally recognized as one of the leaders in the field of compartmentalized cyclic nucleotide signalling in heart physiology.

Building on this ground, the proposed research for the next four years aims at an in-depth analysis of cAMP signalling in pathologic hypertrophy and to the definition of defective cAMP signalling events that underlie heart failure. The team is planning to use both rodent and, crucially, human heart tissue and a combination of genetic, functional, imaging and biochemistry approaches. One of the set aims is to develop new molecules that act as specific activators of PDE to be tested as new therapeutics for heart failure. The studies on cardiac myocytes will be extended to vascular endothelial cells in the attempt to gain a more integrated view of the anomalies affecting the cardio circulatory system. The project is focused and the questions asked are relevant and timely. The team is well equipped both in terms of technology and of human resources to perform the work proposed. However, the possibility to apply the finding of this research to clinical settings appears to be rather uncertain at the moment as the potential therapeutic value of manipulating cAMP in distinct compartments still remains to be proven.

The team seems to miss the opportunity for a closer interaction with the other two teams within the unit to explore some specific aspects of cyclic nucleotide compartmentalization. For example, joining forces with team 1 would place team 2 in a unique position to study the role of compartmentalized cAMP signalling in

mitochondria biogenesis and its impact on heart pathology, an extremely topical area of research within which the combination of techniques and expertise of the two teams would allow to answer important questions.

— Strong points:

- Innovative concepts;
- Strong, cutting edge project pursuing relevant goals and applying state-of-the art technology
- International recognition and strong international interactions.

— Weak points:

- Little interaction with the clinic and still scarce work on humans

- The potential applicability of the compartmentalization concept to the clinic still remains to be proven.

— Recommendations:

- Strengthen the interactions with the other teams within the unit.

Nom de l'équipe : Cyclic nucleotide signaling and cardiac and vascular pathophysiology

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 3 : Small G protein signaling and cardiac pathophysiology

Originally, the group identified a serotonin-activated pathway implicating cAMP, Epac, and two small GTPases (Rap1 and Rac). Interestingly, this pathway is cAMP-dependent but PKA-independent. Because of the importance of cAMP as a second messenger in adrenergic-stimulated cardiomyocytes, it suggested that Epac could also be important in transducing signals during the hypertrophic response in the heart.The team leader demonstrated, therefore, using a variety of techniques in vitro that Epac activation leads to cardiomyocyte hypertrophy. In part, Epac controls the development of hypertrophy via cross-talks with other known hypertrophic pathways. Future directions will involved the assessment of the role of Epac in vivo using animal models, the investigation of the importance of Epac in human cardiomyopathies, and the development of Epac inhibitors that could prove useful in the treatment of heart failure.

In a few years, this team has obtained a good recognition in the field of cardiovascular research. The discovery of the Epac pathway and the subsequent confirmation of its importance in the development of cardiomyocyte hypertrophy are true achievements. This work significantly contributes to the understanding of the physiopathology of the cardiovascular system, and is recognized as such.

Along these lines,the team has published his work in high impact factor peer-reviewed journals (e.g. : Nature Cell Biology, Circulation Research), whic certainly speaks for itself. The proposed research for the next four years is a good balance between straight-forward approaches to study the role of Epac in vivo, and more risky experiments aimed at identifying Epac inhibitors. Importantly, all techniques are already available in the unit,

and the expertise is present. Furthermore, the team leader can take advantage of different core facilities that were established in his institution in the past years (« Transcritomics and proteomics facility » ; « Animal core facility » ; In vivo functional exploration facility ») as well as a Biotech Company (Myotarget) that has been created to develop drugs targeting Epac. All together, there are little doubts that this research will produce interesting data. Finally, the personnel implicated in this team are composed of experienced workers and younger individuals that should be able to carry on the research projects.

— Strong points:

- Innovation, discovery of a new potential therapeutic target for heart failure,
- Relevance in terms of public health,
- Interesting translational research program,
- Excellent expertise in cellular an molecular biology.

— Weak points:

- No real weak points, the expertise, which could be lacking (e.g., pathophysiological animal models), is present in the unit, or will be obtained via collaboration.

— Recommendations :

- One could recommend to hire more people at the postdoctoral level in the future, to balance somehow the experience in the team.

Nom de l'équipe : Small G protein signaling and cardiac pathophysiology

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+

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

The unit is fully adapted to its organization into 3 teams with dynamic projects and good human relationships. Weekly workshops and seminars are organized; all the Unit members participate to these meetings. The ambitious project would be in line with the recruitment of new post-docs and young researchers and would improve the quality and importance of the obtained results.

6 • Conclusions

The excellent research of this unit significantly contributes to the understanding of the physiopathology of the cardiovascular system.

The scientific production resulting from this Unit is very good in both quantitative (127 published papers between 2004 and 2008) and qualitative (mean Impact Factor: 5.33; 19 papers with an IF>10; and 45 publications with an IF > 5). Most of the articles are published in the best rank of the cardiovascular field. Several ANR, Leducq foundation and EC grants were obtained during the last 4 years period.

The personnel implicated in the Unit are composed of experienced senior and junior researchers and younger students that should be able to effectively carry on the different projects. The recognition of the quality of the research realized in the Unit is also evidenced by the regular invitations of its members as speakers in International Congress.

— Strong points:

Innovative concepts, excellent publications, and excellent expertise in cellular and molecular cardiovascular biology, international recognition and strong international interactions

— Weak points:

No real weak points. One could recommend hiring more people at the postdoctoral level in the next years. The researchers have, in our opinion, not to miss the opportunity for closer interactions within the Unit, for example, joining forces team 1 and team 2.

— Recommendations:

The projects developed by the 3 teams are original and will produce interesting results. However, the potential applicability of fundamental concepts to the clinic still remains to be proven. The ability to stimulate the development of innovative projects does not appear in the team 1. An effort of this team to initiate new interesting translational approach is recommended.

Note de l'unité	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+

UNIVERSITÉ
PARIS-SUD 11

Le Président de l'Université Paris-Sud 11

à

Monsieur Pierre GLORIEUX
Directeur de la section des unités de recherche
AERES
20, rue Vivienne
75002 Paris

Orsay, le 20 mars 2009.

N/Réf. : 70/09/GCo/LM/LS

Objet : Rapport d'évaluation d'unité de recherche
N° S2100012378

Monsieur le Directeur,

Vous m'avez transmis le dix mars dernier, le rapport d'évaluation de l'unité de recherche «Signalisation et physiopathologie cardiaque » - UMR S 769, et je vous en remercie.

L'université se réjouit de l'appréciation portée par le Comité sur cette unité et prend bonne note de ses suggestions.

Les points à améliorer seront discutés avec le directeur d'unité monsieur Rodolphe FISCHMEISTER dans un esprit constructif pour l'avenir de la recherche à l'université.

Vous trouverez en annexe les éléments de réponse de ce dernier.

Je vous prie d'agréer, Monsieur le Directeur, l'expression de ma sincère considération.

Guy COURRAZE
Président

PJ : Commentaires de Mr FISCHMEISTER

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UNIVERSITÉ PARIS-SUD 11

Dr Rodolphe Fischmeister

Professeur Pierre GLORIEUX
Directeur de la section des unités
AERES
20, rue Vivienne
75002 Paris

Châtenay-Malabry, le 17 mars 2009

Dear Professor Glorieux,

We would like to thank AERES and his representative for having selected a panel of renowned scientists. The interaction with the visiting committee was very constructive and helpful. We thank the experts for their very positive appreciation regarding our scientific work, our innovative efforts, and the coherence of our three teams. Their appreciation and comments encourage us to pursue with determination our objectives for the coming four-year period.

Concerning some of the specific comments or recommendations, leaders or Team 1 and Team 2 have expressed their desire to provide the following comments.

Team 1 - The committee has noted a "*weakness in the clinical collaboration*" of our team. This is rather odd, as we ourselves consider our participation in clinical research as one of the strongest points of our activity (see page 67 of our scientific report)! Indeed, Team 1 is involved in a large number of clinical collaborations:

- a multicenter clinical trial (SMARTEX), designed to test the beneficial effect of high versus moderate intensity aerobic exercise training;
- a collaboration with a clinical team in Antwerp concerning the effects of exercise training on substrate utilization in skeletal muscle of CHF patients;
- a collaboration with a clinical group in Paris concerning the impact of diabetes in the muscle responses to exercise in heart failure;
- a collaboration with a clinical team in Norway concerning the impact of exercise training modality on fat and skeletal muscle in patients with metabolic syndrome;
- another collaboration with the Norwegian clinical team on the impact of exercise training on skeletal muscle of COPD patients.

The past efforts of team 1 in collaborative human and clinical projects is attested by 7 publications since 2003. We apologize for not having put enough emphasis on this important aspect of our activity during the site visit.

A more important point concerns the penultimate sentence of the AERES report (page 9): "*The ability to stimulate the development of innovative projects does not appear in the team 1*". This is quite a strong statement which we do not understand in the light of the committee

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report on the activity and projects of our team (page 5-6). How do the committee members reconcile such a negative concluding statement with positive statements such as "*the program is indeed innovative*" (page 6, line 14), quoting the three objectives of our team as "*attractive*" (page 6, lines 20, 24, 31), and how could they emphasise in the list of the strong points of Team 1 "*Innovative hypothesis potentially leading to new therapeutic target*" (page 6, line 40)? We believe there must be a mistake and ask the committee to consider revising the penultimate sentence of the report.

Team 2 - The committee has recommended that our team "*strengthens the interactions with the other teams within the unit*". During the 2003-2008 period, 14 publications (out of a total of 59) of Team 2 were obtained as the result of a collaborative effort with another team within the unit. However, only 3 collaborative publications involved Team 1, while 11 involved Team 3. Therefore, some additional effort needs to be directed towards Team 1 and we agree with the committee proposal that "*joining forces with team 1 would place team 2 in a unique position to study the role of compartmentalized cAMP signalling in mitochondria biogenesis and its impact on heart pathology*". Internal discussions have already led to initiate a collaborative project aimed at exploring the cAMP signalling compartments controlling the activity of the ryanodine receptor, SERCA and the contractile proteins using skinned cardiac myocytes and fibres (team 1) and imaging techniques (team 2). Two second-year PhD students (one in each team) have started to perform common experiments and the collaboration is underway. Concerning the role of compartmentalized cAMP signalling in mitochondria biogenesis, this is part of an ANR application led by a researcher in Team 1 and the project, if funded, will also involve Team 2.

Yours sincerely,

Rodolphe FISCHMEISTER
Director UMR-S 769

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