Signalisation et physiopathologie cardiovasculaire

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Signaling and cardiac pathophysiology

Under the supervision of the following institutions and research bodies:

Université Paris-Sud

Institut National de la Sante Et de la Recherche Médicale - INSERM

February 2014

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

Department for the evaluation of research units

On behalf of AERES, pursuant to the Decree of 3 november 2006[1]*,*

- Mr. Didier HOUSSIN, president
- Mr. Pierre GLAUDES, head of the evaluation of research units department

On behalf of the expert committee,

- Mr. Joël NARGEOT, chair of the committee

[1] The AERES President "signs [...], the evaluation reports, [...] countersigned for each department by the director concerned" (Article 9, paragraph 3 of the Decree n ° 2006-1334 of 3 November 2006, as amended).

Evaluation report

This report is the result of the evaluation by the experts committee,the composition of which is specified below. The assessments contained herein are the expression of an independent and collegial deliberation of the committee.

Unit name:	Signaling and cardiac pathophysiology
Unit acronym:	
Label requested:	UMR_S
Present no.:	UMR_S769
Name of Director (2013-2014):	Mr Rodolphe FISCHMEISTER
Name of Project Leader (2015-2019):	Ms Ana Maria GOMEZ GARCIA

Expert committee members

Chair:	Mr Joël NARGEOT, Université Montpellier
Experts:	Mr Flavien CHARPENTIER, INSERM, Nantes
	Mr Thierry COUFFINHAL, INSERM, Pessac
	Mr David EISNER, University of Manchester, United Kingdom
	Mr Dominique ELADARI, INSERM, Paris (representative of CSS INSERM)
	Mr Derek HAUSENLOY, University College London, United Kingdom

Scientific delegate representing the AERES:

Mr Patrick LACOLLEY

Representatives of the unit's supervising institutions and bodies:

Mr Etienne AUGÉ, Université Paris-Sud

Ms Leïla BEN JANNETTE, INSERM

Mr Yves LEVI, Paris, Université Paris-Sud

Mr Marc PALLARDY, Faculté de Pharmacie, Université Paris-Sud (representative of Doctoral School n°425 "innovation thérapeutique: du fondamental à l'appliqué")

1 • Introduction

History and geographical location of the unit

The UMR-S 769 is composed of 45 persons, including 7 researchers (4 INSERM and 3 CNRS), 10 faculty members (2 PU, 7 MCU and 1 ATER), 10 engineers and technicians (including 3 in temporary position), 5 postdocs and 11 doctoral students, plus a few students doing their internship

It occupies a surface of 1200 m^2 coresponding to the entire 2nd and 5th floors and half of the 3rd floor of the D4 building in the School of Pharmacy in Chatenay Malabry. The PI in charge of the former team 3 (G-protein signalling and cardiac pathophysiology) moved at the end of 2010 in Toulouse to join UMR-S 858. In the same period two PIs moved from Montpellier (U 637) to Châtenay Malabry and joined UMR-S 769 to create and lead the new team 3 in January 1, 2011: "calcium signalling and cardiac pathophysiology"

The unit is affiliated to the Université Paris-Sud since 1992 and UMR since 1998. 11 people working in the lab are fully employed by the university (9 Faculty + 2 Technical staff).

The unit is also affiliated to the CNRS.

Management team

The lab will be directed by Ms Ana Maria GOMEZ GARCIA. She will be seconded by a deputy director. Financial and administrative issues will be handled by the Administrative Assistant.

A Strategic committee will be constituted by the director, the deputy director, and all other team leaders. This experts committee will meet on need, to discuss about strategic issues that may affect the laboratory structure (e.g. new teams, new faculty positions or recruitments, etc.).

Each team is co-directed by 2 team leaders. Each team organizes their own meetings.

The Laboratory Council is formed by all laboratory members and meets once a week. Once a year, in January, this meeting will serve as a General Assembly. Moreover, the laboratory will have one seminar a month in the lab by an invited scientist, plus one seminar a month at the IFR 141 (les "Lundis de l'IFR") and one every two months at the LabEx LERMIT (International Chair of Therapeutic Innovation).

AERES nomenclature

SVE1_LS4

Unit workforce

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	10	11
N2: Permanent researchers from Institutions and similar positions	6	5
N3: Other permanent staff (without research duties)	7	7
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	1	
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	7	11
N6: Other contractual staff (without research duties)	1	2
TOTAL N1 to N6	**32**	**36**

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	9	
Theses defended	22	
Postdoctoral students having spent at least 12 months in the unit	14	
Number of Research Supervisor Qualifications (HDR) taken	4	
Qualified research supervisors (with an HDR) or similar positions	12	12

2 • Overall assessment of the interdisciplinary unit

The unit composed of three teams aims at understanding the mechanisms of cardiac pathophysiology in particular the mechanisms governing the transitions between normal heart to hypertrophy and heart failure. They share different animal models that they explore at the molecular or in vivo levels under different aspects such as alterations of the electrical activity focusing in particular on calcium fluxes, contractility of cardiomyocytes or of the whole heart (ex vivo and in vivo) and the development of arrhythmias related to the pathology of heart failure or to the genetic mutations of ion channels (CPVT).

The research of all teams has led to major results in basic research to understand physiological aspects of the regulation of cardiac function by energy metabolism, cyclic nucleotides, phosphodiesterases, calcium signalling. Development of new innovative technological tools and new concepts arising from this basic research were published in very good and excellent international journals. The contribution to cardiac pathogenesis of these newly identified targets has been explored in appropriate animal models. The unit includes a large proportion of faculty professors having a high implication as well as full time researchers in management, teaching and training PhD students and undergraduates and welcoming postdocs. The unit develops original projects with a very good balance between continuation of previous programs in molecular cardiology around the key words “energetic metabolism, cyclic nucleotide and PDE signalling, calcium signalling and ion channels” and new developments including original mouse models. The project is characterized by the addition of a vascular axis and a clear orientation towards pathophysiology in particular heart failure with innovative hypothesis and original tools such as the platform (Ciblot) to screen for drugs on their identified targets. New more risky programs obtained promising preliminary results and are already supported by fundings during the next years. An increase of the translational activity is attested by the promotion of new collaborations with clinicians. In conclusion, excellent and attractive research unit.

Strengths and opportunities related to the context

- quality and number of very good to excellent publications (152 with 16 % with IF> 9 and 45 % with IF > 5 and over 1000 citations in 2013);

- very good balance between continuation of successful projects and new innovative and risky programs most of them being already supported by grants (ANR or private);

- international recognition in molecular cardiology of senior members attested by large number of invited conferences (over 140) including international standards (gordon conferences) and distinctions/awards;

- members of prestigious national and international networks also as coordinators (Leducq fondation: 2006-2012, EugeneHeart: 2006-2010, LabEx LERMIT: 2011-2019);

- high funding capabilities in very competitive applications;

- outstanding teatching and training activities associated with the promotion of the interface between drug chemistry and biology;

- development of translational studies with an increasing implication of clinicians (PHRC, Cohort CPVT, relation with DHU, etc.);

- ambitious perspectives in therapeutic developments via drug screening and ambitious perpectives in academic programs in the future (integration in the project Université Paris Saclay).

Recommendations

It is recommended to support and train the best students for the recruitment of a new full time researcher in particular in team 1. The excellence of the unit should also attract new researchers from other institutions as already done with the group of the future director

3 • Detailed assessments

Assessment of scientific quality and outputs

The goal of the unit is to understand the normal and pathological function of the heart. The studies are dedicated to the main functions of cardiomyocytes such as excitation-contraction coupling, contractility and energetic metabolism and their integration in the whole heart. The pathological studies mainly concern Heart Failure (HF), one of the most frequent human diseases for which the exact mechanisms leading first to the transitions towards compensated hypertrophy and then to heart failure still remain unknown. Also, as well as affecting contractile function by many pathways, HF is also characterized by the development of lethal arrhythmias attributed to an alteration of intracellular calcium homeostasis.

The functional approach includes electrophysiological measurements associated to biochemical, pharmacological, and molecular approaches, and in vivo experiments in the whole animal. They have been extended more recently to vascular tissue to investigate cardiovascular physiology from molecular to integrated level. A particular focus is oriented on calcium signaling at the plasma membrane level (L-type calcium channel), sarcoplasmic reticulum level (RYR2) and nucleus/mitochondria with studies of compartmentalization of cyclic nucleotides and energetic regulation pathways (synthesis, utilisation). These dynamic compartments include also phosphodiesterases (PDEs), membrane receptors signalling pathways in their modulation of excitation-contraction and transcription coupling. The ultimate goal of the different teams is to study the role and importance of these different signalling pathways and dynamic compartments in the pathogenesis of heart failure and other cardiac pathologies and to screen for molecules of therapeutic interest.

The unit is organized in three teams with similar pathophysiological goals using complementary approaches:

- team 1: Energy signalling and cardiac and muscle pathophysiology;

- team 2: cyclic nucleotides signalling and cardiovascular pathophysiology;

- team 3: calcium signalling and cardiac pathophysiology.

By complementary approaches the three teams have been able to provide major data in this field. Among them, the main breakthroughs include:

- the demonstration of impaired energy metabolism during HF: depressed energy production, altered energy transfer and impaired energy utilization;

- evidence for energy compartmentalization in cardiomyocytes;

- development of the concept of “metabolic therapy” with PGC-1α as a potential target and investigation of the role of AMPK in doxorubicin-induced cardiomyopathy and SIRT1 in the ER stress response;

- cAMP compartmentalization of PDEs in cardiac myocytes: PDE3 and PDE4 are reduced in cardiac hypertrophy;

- PDE4 regulation of cardiac EC coupling, calcium homeostasis and arrhythmias in animal ventricular cardiomyocytes and human atria;

- role of cGMP-stimulated PDE2 in heart failure: up regulation of PDE2 during HF is cardioprotective against β-adrenergic toxicity;

- nuclear and mitochondria cAMP/PKA signalling;

- role of intracellular calcium related to RYR2 mutations in arrhythmias in CPVT;

- increased expression of Epac in HF via stimulation of Excitation-Transcription coupling;

- cardioprotective role of the RYR2-accessory protein FKBP 12.6: role of L-type calcium channel and regulation via Epac;

- the demonstration that Aldosterone or the overexpression of the mineralocorticoid receptor (as observed in heart failure) induces a down-regulation of FKBP 12.6.

Over the period of the contract, the unit has produced 152 original publications, 38 reviews, 15 book chapters and provided 380 abstracts in meetings. Two patents have also been produced. The mean impact factor for the original publications is 5.64 and among them 29 publications have an IF >9 and 85 publications have an IF>5. The excellent journals with very high impact factor include: Circulation (6) JACC (3), JCI (3), Circ Res (8). Concerning the citation index, citations (each year) increased from about 500 in 2006 to reach 1000 in 2013.

Overall, the production of the unit and lab member can be considered as excellent.

Assessment of the unit's academic reputation and appeal

The UMR-S 769 is internationally recognized for its expertise in several areas of cardiac pathophysiology:

- unique expertise in energy metabolism (cardiac and skeletal muscle) in France and very good international position in this field;

- outstanding international recognition in the field of membrane signalling associated to cyclic nucleotides and in cardiac cells;

- excellent international recognition in the field of calcium imaging (calcium sparks analysis), intracellular calcium homeostasis in cardiac excitation-contraction and excitation-transcription coupling.

This excellent international reputation is attested by various indicators:

- large number of invitations to conferences (including 4 Gordon conferences) and seminars: 143 invited conferences and 57 seminars;

- strong national and international collaborations (5 in America, 16 in Europe, 3 in Africa, 2 in Asia) including being coordinators for prestigious funded networks (Leducq fundation, EUGeneHeart, Labex Lermit);

- prizes and distinctions (5): Edouard Coraboeuf , FRM cardiology award, Alain Castaigne Prize (fellow ISHR, invited professorship, etc.);

- membership in scientific committees: Inserm (member and president elected), CNRS (conseil Scientifique), Université Paris-Sud, ENS Cachan;

- elected council members (5): Biophysical Society, European Working Group in Cardiac Electrophysiology, Groupe de Reflexion sur Recherche Cardiovasculaire, International Society for Heart Reseach, Société de Biologie, etc;

- members of Editorial Boards (4): Cardiovasc Res (IF 5.9), Journal of Molecular and Cellular Cardiology (IF 5.1) Eur J Heart Fail (IF 5.2);

- attraction of a large number of students and post docs from France and abroad (Norway, Belgium, Poland, Canada, Estonia, Czech Republic, Croatia, Slovak Republic..) and obtention of the funds required;

- meeting organisations (6): European Section of Aldosterone Council meeting, Biophysical Society Meeting, European Working Group for Cardiac cellular electrophysiology, EUGeneHeart network, European Society of Cardiology-Heart Falure Association: meeting etc.

Assessment of the unit's interaction with the social, economic and cultural environment

The creation of the unit on this site has attracted new Inserm or CNRS units and promoted the site of the School of Pharmacy of the Université Paris-Sud. The creation of the UMR-S 769 has been followed by a strong stimulation of the interface between chemistry (dominant activity of the site previously) and biology with the creation of platforms including one for the screening of new therapeutical drugs (Ciblot), by initiating and obtaining the Labex LERMIT which gathers 15 laboratories and by ambitious projects for the unit in the future such as the relocation of these laboratories in a large campus in a few years (Université Paris Saclay: UPSay):

- involvement in two patents and one industrial contract (Sanofi) and transfer of technology from LERMIT to Big pharmas;

- various popularization activities (fête de la science, actions targeted to broad audience, interviews, popular articles, etc.);

- participation in events on gender medicine;

- welcoming of college students.

Assessment of the unit's organisation and life

The organisation of the unit is very impressive with a very high involvement of the different members of the technical staff: secretaries, technicians, engineers in charge of all aspects of the life of the unit (management of expenses, animal facility, seminar organisation, etc.). The visit and the interviews with technical staff showed that the tasks and responsibilities are clearly defined and that each member of the unit is fully responsible for one or more specific tasks.

A lab meeting is organized every Monday morning which everybody attends, during which all problems of the lab can be discussed and solved. It is also an opportunity for students to give presentations of their work. Although each team raises funds from various sources, the part corresponding to running costs (current expenses as chemicals, consumables, supplies, animals, etc.) is more or less globalized to avoid duplicates and to rationalize. Matters such as congress attendance, new projects or strategies such as production of adenovirus constructs for instance are discussed in these meetings. A special request for a "general assembly" can be presented by members (generally in January after notification of budget by INSERM), also for costly equipment or investments (for instance making a transgenic mouse). A provisional budget is presented for the year by the secretary very highly involved in the management of the unit and who can be considered in the US system as a lab manager, in close relation with the director and able during his absence to make a rapid decision for current functioning of the laboratory. A projection of the current expenses can be done from previous year which allows an estimation of the possible investments during the year. A similar meeting is planned in June (after ANR results) to update the financial situation.

Regular team meetings occur (on average once a month) and one seminar a month is organized by IFR 141 (lundis de l'IFR). One to two invited seminars are organized by the unit each month. A seminar every two months is organized by the labEx LERMIT headed by the director, and each year a "journée recherche" is organized by IFR which allows junior researchers, post docs and PhD students to present their work. In addition, the Doctoral School (ED n°425) has an annual meeting devoted to presentations by PhD students. Finally a retreat of two days was organized in October 2012 to plan the new project and strategy for the next renewal of the unit and to discuss about the new organisation.

Assessment of the unit's involvement in training through research

The unit is composed of 10 tenured faculty members mainly at the school of pharmacy in the Université Paris Sud (actually 3Pr and 7 MCU and 1 MCU position opened for September) and highly involved in teaching (about 50 % of their time). The unit belongs to the Doctoral School ED n°425 "innovation thérapeutique: du fondamental à l'appliqué". The large involvement of the members in the life of the ED has been underlined by the director of the ED during the exchange with the expert committee members. ED is divided in 7 poles, and one "physiopathologie Moléculaire et Cellulaire" was recently taken by a PI of team 2. One is professor of physiology (team 3) at the faculty of medicine of Paris-Diderot university and coordinates the master 2 "biology, physiology and pharmacology of circulation and respiration" common to several universities (Paris-Descartes, Paris-Sud, Paris-Diderot, Paris Nord, and Paris-Est). In this master, 2 PI of team 2 are responsible for teaching units: UE 1 (Biology, Pathophysiology of heart Rhythm) and UE 3 (Normal and pathologic cell signalling), 2 PI of team 3 responsible for UE2 (Biology, Pathophysiology of excitation-contraction-relaxation coupling) and a member of team 1 is responsible for UE4 (Biology, pathophysiology of cardiac metabolism). 2 PIs (team 1 and team 2) have developed an e-learning module and created a teaching unit aimed at attracting young pharmaceutical students into the field of research. In another master of Université Paris-Sud and U Paris Est, "pharmacology, pharmacokinetics and pharmacogenetics" a PI of team 2 coordinates the UE "cardiovascular pharmacology". In the master "Pharmaceutical Biotechnology and Innovative therapies" (Univ Paris 5,7, Université Paris-Sud) a PI of team 3 is in charge of "Gene therapy" and "research" as well as "therapy side effects : from pathology to Therapy" in the DU "Integrated thoracic Oncology"). Overall all PIs from each team are largely involved in teaching in master 2 in the different universities of Paris and in the Université Francois Rabelais in Tours.

Training events such as summer school are also organized. Ten PIs have HDR (4 have been obtained during the contract) and have trained 22 PhD students (11 are ongoing). Many post-docs were trained during the 2008-2013 period (14) and 9 are ongoing. One can also note the large number of undergraduate (M2, M1, L3) who have been trained by the different teams (total over 30). The different Teams also welcomed foreign students and post-docs from different countries (Italy, Morocco, Spain, Ivory Coast, China, Slovakia, Brazil, etc.) and several visiting

professors (Estonia, Mauritius, Cuba, Brazil, etc.). Collaborative research networks favour exchanges of students and participation to international training programs as well as the symposia organized by the LabEx LERMIT.

Assessment of the strategy and the five-year plan

The new unit UMR-S 769 "Signalling and Cardiovascular pathophysiology" will be headed by Ms Ana Maria GOMEZ GARCIA and will be still composed by three teams:

- team 1: Energetic signalling and cardiovascular pathophysiology;

- team 2: Cyclic nucleotide Signalling and Cardiovascular pathophysiology;

- team 3: calcium signalling and Cardiovascular Pathophysiology.

The key words of the project clearly indicate the specificity of each team (energy, cyclic nucleotide and calcium) while signalling and pathophysiology indicate that the unit share common goals. In addition, this new project is also oriented towards cardiovascular physiology and pathophysiology with the development of new projects devoted to vascular tissues and cells. The orientation towards translational research and pathophysiology is attested by the presence of clinicians in the unit and the clinical relationships that have been established with several hospitals on heart failure (Antoine Beclère and Bichat), pulmonary hypertension (Centre chirurgical Marie Lannelongue, Bicêtre), cancer therapy (Institut Gustave Roussy, Antoine Béclère) by members of the three teams.

The different projects of the new unit are complementary and with a very good balance between continuation of previous studies and development of new innovative more risky projects. The ultimate common goal is to decipher mechanisms involved in the pathogenesis of heart failure (HF) and some other cardiac pathologies for instance related to genetic mutations (CPVT) or to cardiac toxicity associated to treatments of other pathologies (cancer).

In this context the main directions of the scientific project concern:

- mitochondrial life cycle and dysfunction in HF;

- mitochondrial dynamics including ER stress, mitophagy and apoptosis and the role of targets identified (PGC-1α) based on the novel and emerging concept of a major role of energy failure in the pathogenesis of HF;

- metabolic therapy in HF based on screening molecules via the Ciblot platform of the unit to promote mitochondrial biogenesis and in particular activators of PGC-1a on which converge many receptor-dependent pathways (AMPK and Sirt1);

- intracellular organisation of cyclic nucleotide pathways in cardiac and vascular cells and their alterations in heart failure;

- compartmentalization of cyclic nucleotide signalling: studies will assess intranuclear and mitochondrial cAMP/PKA or cAMP/Epac pathways in cardiovascular cells, spatiotemporal control of Epac and GMPc signalling, contribution of new Phosphodiesterases (PDE1,8,9 and 10), study the Intracellular cAMP compartmentalization and exploring the idea, by an innovative approach based on nanoparticules immobilizing ligands, that localisation of ion channels or receptors at specific sites (Membrane, T-tubules, caveolae) impact their physiological function by recruiting different partners. This program benefits from a close collaboration between biologists of the unit and chemists of the site the through LabEx LERMIT;

- development of studies focused on vascular muscle with the idea to investigate on VSMC in vitro or ex vivo in a first step how the crosstalk between endothelium and VSMC impact the function of PDEs, downstream effectors of cAMP with a focus on Ca regulators and contribution of Epac and PKA in regulating the vascular tone;

- **regulation of EC-coupling by cAMP pathway,** the specific aim is to identify the nature of PKA (I or II) in the regulation of L-type calcium channel in cardiomyocytes;

- looking for new therapeutic strategies on PDE based on previous studies that PDE4 deficiency deranges calcium homeostasis and leads to ventricular arrhythmias, cardiac overexpression of PDE4 and PDE2 in mouse will be realized to investigate the impact in the development of HF or overexpression of the β-adrenergic pathways. Studies on the interaction between cyclic nucleotides and calcium signalling will benefit from the expertise of two teams (2 and 3);

Again, the development of a therapeutic application will arise from a close interaction with chemists of the LabEx LERMIT and the Ciblot platform since screening for PDE activators is an important aspect of the project.

Moreover and of clinical interest, the expression profile of the β-adrenoreceptor/cAMP/PDE pathways will be investigated in lymphocytes also from patients, thanks to the clinicians associated to the team and to the collaboration with the Département Hospitalo Universitaire (DHU) Torino, to look for this pathway in terms of a biomarker of HF severity;

- elucidate the roles and the mechanisms of Ca fluxes alterations in the transition of cardiac hypertrophy/heart failure and the generation of arrhythmias. Following the identification of a major role of the RYR2 receptor and of the associated protein FKBP12.6 in the genetic cardiac pathology CPVT using a mouse model, a new original knock in mouse with a mutation of RYR2 in N-ter has been produced. As a translational approach, cardiomyocytes derived from patients-induced stem cells (iPSC) ie obtained from fibroblasts of patients (through a collaboration with clinicians in Spain) and derived in CM by an expert laboratory in USA or a private company (Cellular Dynamics). The cardioprotective role of FKBP 12.6 will be studied in vitro (using iPSC) and mice (possibility of rescuing CPVT phenotype or cathecholamines-dependent arrhythmias). Following on from this project it is proposed to screen for drugs able to mimic the role of this protein and again a collaboration with the platform Ciblot is planned;

- elucidate the mechanisms underlying the role of Aldosterone in HF, aldosterone is known as a major actor of HF in which the MR receptor was shown in previous studies of the group to upregulate L-type calcium channel. In an innovative project, It will be studied if MR directly regulate transcription of Cav1.2 using a model mice in which the luciferase gene is under the control of the Cav1.2 promoter. High throughput approaches will also be used in collaboration. New targets of aldosterone will be investigated through this collaboration using Chip-seq. In addition the role of SOC channels (TRPC and Orai) will be investigated. In relation with these studies, it will also be investigated whether the effect of Epac, which induces hypertrophy and potentiate calcium signalling not through L-type calcium channel, may act through other actors such as TRPC, Stim or Orai to stimulate excitation-transcription coupling;

- investigating heart failure induced by anticancer therapy, the aim is to identify the signalling pathways cascades involved in cardiotoxicity of anti-cancer molecules such as doxorubicine associated or not to radiotherapy. This is both a recent topic developed in the unit and also a model of cardiac failure in the context of cardiac pathophysiology, a common aim to all the teams. This is an important health problem and the goal is to identify targets as potential therapeutic agents. Experimental models of chemo/radiotherapy are used *in vitro* and *in vivo* and cardiac function will be investigated. The fisrt step is to focus on Epac signalling, also by using KO mouse for Epac as well as other models in which a tumor has been engrafted explored by several approaches using electrophysiology and confocal microscopy (Ca handling).This program is quite ambitious and will be developed in collaboration between the different teams;

Overall, the different projects are tightly linked in terms of therapeutic goals and the different approaches specific to each team appear by their complementarities as a strength promoting the development of collaborations between teams which increases the feasibility of the whole project. The networks developed on the site, the collaborations between biologists and chemist through the IFR or LabEx LERMIT and the Ciblot platform reflect the dynamism of the unit and its members and appears as major element for the success of the research program in the coming years. The expertise of the members of this laboratory and the quality of the research is attested by many indicators (publications, invitations, collaborations, funding) and their implication in teaching and training is also excellent with ambitious projects planned at the end of the next contract (2014-2019) when the unit will be relocalised joining the new campus UPSay.

4 • Team-by-team analysis

Team 1: Energy Signaling and Cardiovascular Pathophysiology

Name of team leader: Mr Vladimir VEKSLER & Ms Anne GARNIER-FAGART

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	3	4
N2: Permanent EPST or EPIC researchers and similar positions	2	
N3: Other permanent staff (without research duties)	1	1
N4: Other professors (PREM, ECC, etc.)	1	
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	4
N6: Other contractual staff (without research duties)		1
TOTAL N1 to N6	**10**	**10**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	2	
Theses defended	5	
Postdoctoral students having spent at least 12 months in the unit	4	
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	4	4

• Detailed assessments

Assessment of scientific quality and outputs

Research by team-1 has led to important advances in the field of chronic heart failure. The PIs of team N° 1 are established scientists who have contributed several important results in cardiology. Heart failure is one of the most frequent human disease. However, the exact mechanisms leading to cardiac dysfunction and ultimately HF are still not completely solved. This team has contributed to develop the concept that HF results, at least partly, from

depressed energy production, altered energy transfer, and impaired energy utilization. For that reason the work of team 1 during the last four years has consisted in:

1) deciphering the mechanisms of energy compartmentation and mitochondrial dynamics in cardiomyocytes;

2) the demonstration of impaired energy metabolism during HF.

These two first steps have led them to develop strategies that aim at improving energy metabolism during HF and at what they call "metabolic therapy".

Quality of research by this team is illustrated by 57 publications during the previous 5 years period. Among these publications 28 originate from the team itself, 17 are collaborations with a major input of the members of the team (members are either second or penultimate authors) and 12 are participation of studies from other groups. Most of the studies are published in very good journals from the speciality such as Circulation Heart failure, J Cell Science, PloS One, Cardiovascular Research, Journal of Physiology, etc (top 40 %). And the average impact factor of publications from the team (list 1) is 4.79. Noteworthy, this production has been performed by a group composed by only 1 full time researcher and 3 faculty members with only 50 % of their working time dedicated to research because of their intense teaching duties. Also the large number of collaborative studies attests from their unique expertise in an important field and from intense efforts of collaboration.

Assessment of the unit's academic reputation and appeal

This team is internationally recognized for its unique expertise in energy metabolism and muscle function. Only few groups in the world share same expertise in this field in which it is quite difficult to publish in very high impact journals while the community does agree that it is an important aspect of cardiac dysfunction. All members of the team are regularly invited to give lectures in national or international meetings (64 invited conferences).

Members of the Team are regularly reviewers for the best journals of the speciality and are members of editorial boards (Circulation Research and Frontiers in Physiology). One member is part of the "Conseil Supérieur de la Recherche et de la Technologie" from the Ministry of Research.

As already stated above the large number of collaborative studies attests from their unique expertise in an important field. This includes the participation to the EUGeneHeart network (2006-2010).

The groups is also clearly attractive as attested by the large number of students and post docs from France and abroad (Norway, Belgium, Poland, Canada, Estonia, Czech Republic, Croatia, Slovak Republic) that have been trained.

One other point attesting the academic reputation of the team is their very good ability to obtain funds particularly to improve their equipment and to support post-docs and PhD students positions. Among the different fundings obtained, the very competitive FRM (250 k€), the supervision of one workpackage of the LabEx LERMIT, and the participation to the EUGeneHeart program are noticeable.

Assessment of the unit's interaction with the social, economic and cultural environment

- one of the team leader is an invited professor in Estonia and Mauritius;

- the team is also member of a LabEX (LERMIT);

- members of the group have organized two national workshops and participated actively to the creation of the CNRS network Meetochondrie;

- all members are regular members of national and international steering committees;

- actions targeted to a broad audience such as TV appearances are elements of interaction far beyond academic communication.

Assessment of the unit's organisation and life

Very good organisation in agreement with the unit organisation.

Assessment of the unit's involvement in training through research

Due to the fact that 3 members of the team are tenured faculty members and one is faculty with a temporary position (ATER), all members of the team are actively involved in both teaching and training. For example, both team leaders are involved in teaching Physiology, anatomy, embryology but also endocrinology and neurophysiology to the Pharmacy students. One leader is also involved in the development of e-learning.

Beyond their academic teaching duties, members also participate actively in teaching for graduate students at Paris Descartes and Paris Diderot and have in charge the supervision of teaching cardiovascular metabolism at the M2 "Biologie et physiopathologie cardiaque".

3PIs have the HDR and train PhD candidates regularly.

Since 2008, Team 1 has trained 3 M2, and 5 PhD students. Presently 2PhD students are trained.

Assessment of the five-year plan and strategy

The five-year plan will focus on three research themes which prolong and extend the work done so far:

- **Mitochondrial life cycle and dysfunction in HF**

The researchers intend to investigate the role of several different aspects of the mitochondruial life-cycle in the setting of cardiac dysfunction. These include PGC-1α, mitochondrial dynamics, ER stress, mitophagy, and apoptosis in cardiac failure. All of these are important and emerging area in heart failure research and should lead to important new mechanistic insight into the role of mitochondria in heart failure.

- **Regulation of Mitochondrial life cycle and function by AMPK and SIRT1**

The researchers intend to investigate, using a variety of experimental models, the role of AMPK and SIRT1 in the regulation of the mitochondrial life cycle and function in heart failure through the modulation of PGC-1α. They will explore the interplay between these two factors and specifically investigate the role of AMPK in doxorubicin cardiomyopathy and SIRT1 in the ER stress response. This important and interesting work should result in the identification of novel targets for treating heart failure.

- **Metabolic therapy and HF**

In this section, the researcher intend to screen for new activators of PGC-1α as a therapeutic strategy for treating heart failure by promoting mitochondrial biogenesis in order to compensate for energy starved cardiomyopathic heart. This section of work should result in novel activators of PGC-1α which may then be tested as new treatments for heart failure.

- **Overall assessment of the program of team 1**

Overall, there is no doubt that this team has a good project which might help the team to be very well ranked at both national and international level. There is clearly a good potential for future translational developments. The aims are focussed, and the scientific questions appear importants and logically organized. The strategies described are based on a strong scientific background, with collaborations and innovative technologies as needed. The group has good funding, particularly to support the investments in new equipment and the development of the new technologies required.

However, one potential threat is that most of the group, except one researcher emeritus, is composed of Faculty members with very strong involvement in teaching. Therefore, the project might be slow down and a solution has to be find to allow the recruitement of full time researcher(s).

Conclusion:

- **Strengths and opportunities:**

Experienced and distinguished leader and associates. Very unique expertise in an important but difficult field which has to be maintained in France;

Research projects are at good international level;

Strong preliminary work, established protocols, and knowledge;

Focused projects, based on relevant scientific and clinical research questions;

Very unique expertise in mitochondrial function and energy metabolism, an important but difficult field, which has to be maintained in France;

Established collaborations in France and other European countries.

- **Weaknesses and threats:**

Watch out for overload by excessive teaching duties;

Publication in the past were limited to journals of the specialty. However, there is a clear potential of the proposed research to reach a broader audience.

- **Recommendations:**

The number of PIs fully dedicated to research is not sufficient. However, the situation will be initially balanced by the recruitement of 3 post docs (funding obtained) among which the whole lab have identified a good candidate for potential recruitement as "Chargé(e) de Recherche";

Continue efforts to valorize the research considering there is a very good potential.

Team 2: Cyclic Nucleotide Signaling and Cardiovascular Pathophysiology

Name of team leader: Mr Grégoire VANDECASTEELE & Mr Rodolphe FISCHMEISTER

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	4	4
N2: Permanent EPST or EPIC researchers and similar positions	3	3
N3: Other permanent staff (without research duties)	2	2
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	1	3
N6: Other contractual staff (without research duties)	1	1
TOTAL N1 to N6	**11**	**13**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	4	
Theses defended	11	
Postdoctoral students having spent at least 12 months in the unit	4	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	4	4

- ## Detailed assessments

Assessment of scientific quality and outputs

Research projects developed by team 2 are based on an excellent expertise on the roles of cyclic nucleotides in cardiac function under physiological and pathophysiological conditions (such as cardiac hypertrophy, heart failure and arrhythmias). Studies during the past 6-year period (2008-2013) were focused mainly on the role of cellular compartmentation of phosphodiesterases in the regulation of cardiac contraction and arrhythmias through a "molecular-to-whole animal" approach (transgenic mouse models). The main results are:

- the identification of Phosphodiesterase (PDE) 4B as the main PDE controlling the β-adrenergic stimulation of the L-type Ca2+ current and cardiac contraction;

- the demonstration that PDE4 is an important regulator of human atrial electrical and contractile activity and that a decreased expression of PDE4 may promote atrial fibrillation;

- the demonstration that the expression of PDE3 and PDE4 decreases during cardiac hypertrophy;

- the demonstration that, in contrast, the expression and function of PDE2 increases in heart failure, and may constitute a protective mechanism.

This was asociated by technical breakthrough developped to probe intracellular organisation of cyclic nucleotides (FRET-based techniques and use of CNG channels).

In parallel, the recruitment of 2 faculty members allowed the development of a new project aimed at characterizing the role of PDE isoforms in cAMP compartmentation in vascular smooth muscle cells.

The outstanding quality of the research performed by this team is illustrated by their excellent level of publication. During the previous 6-year period (2008-2013), the team has published 69 original articles and 14 review articles in peer reviewed referenced journals such as Journal of Clinical Investigation, Journal of the American College of Cardiology, Circulation, cardiovascular Research, etc. as well as 5 book chapters. Among the 83 peer reviewed articles, 42 originate from the team himself (11 with IF> 10; average IF = 7.05), 14 are collaborations with a major input of the team members (second and/or penultimate author) and 27 are collaborative publications with lower input. The large number of collaborative studies attests to the expertise of the team.

The team also shows an excellent capacity to be funded: 2 international networks (PI), 9 national public grants (8 as PI) and many university, regional of private grants.

Assessment of the unit's academic reputation and appeal

The team is world-leading in its expertise in the field of membrane and intracellular signalling associated to cyclic nucleotides in cardiac cells.

Since 2008, the team members have been invited 96 times to give lectures in national and international meetings and seminars. They also co-organized 3 symposia.

The team has been involved in 10 national and 3 international scientific project networks as partners (3) or leaders (10). They established 13 national and 18 international collaborations in addition to those established within the two international networks they belong to, i.e., the "EUGeneHeart" EU-FP6 large-scale network (21 laboratories) and the "cycAMP" Leducq foundation transatlantic network of excellence (11 labs), coordinated by one of the team co-leaders, Mr Rodolphe FISCHMEISTER.

Two team members received a national prize (Award E. Coraboeuf and JJ Beziat) and one was also elected to Fellowship of the International Society for Heart Research.

Members of the team are regularly reviewers for excellent journals. One of the team co-leaders (RF) has been/is the associate editor of 3 journals including Cardiovascular Research.

All those facts attest to the outstanding national and international recognition of the team. They also explain the attractiveness of the team: 3 faculty members, 1 CNRS research scientist and 1 engineer joined the team in the past 5 years.

Assessment of the unit's interaction with the social, economic and cultural environment

Since 2008, the team 2 has produced two patents and has been involved in one industrial contract.

One of the co-leaders (RF) founded and is now coordinating the LabEx LERMIT, in which the team is highly involved.

All team members are regularly involved in national and international steering and evaluation committees. Mr Grégoire VANDECEASTELLE was elected in the administration council of the Groupe de Réflexion sur la Recherche Cardiovasculaire, French Society of Cardiology, and RF in the European Council of the International Society for Heart Research. RF has been president of an Inserm Scientific Committee (CSS4) from 2008 to 2012.

The team has been involved in different popularization activities (Fête de la Science, articles, interview).

Assessment of the unit's organisation and life

The team is well organized to deal with the project with a good balance between researchers and technical staff. The team leaders have fostered two new groups, one on vascular physio/pharmacology and one on mitochondria.

Assessment of the unit's involvement in training through research

Four members of the team are tenured faculty members from the Université Paris-Sud, and are therefore highly involved in teaching, spending approximately 50 % of their time teaching pharmaceutical or medical students. Among them, 2 are developing an e-learning module and creating a teaching unit aimed at attracting young pharmaceutical students to the research field. However, all PIs regularly teach in Master 2 in different universities (Paris-Sud, Paris-Descartes, Paris-Diderot, François Rabelais in Tours); 2 of them heading M2 teaching units. The team also organizes training events such as summer schools and symposia through the LabEx LERMIT.

Four PIs have the HDR (authorization to lead research) and train PhD candidates regularly. Since 2008, 8 students (including one in co-supervision with the Chinese Academy of Sciences in Beijing, China) obtained their PhD. The team has also welcomed foreign doctoral students (from Italy, Morocco, Ivory Coast) in the context of collaborative studies. Five PhD theses are ongoing. Three post-docs have been trained.

Since 2008, the team has also trained 18 M2, 7 M1 and 11 L3 students for training.

Assessment of the strategy and the five-year plan

During the next five-year period, team 2 will explore more deeply how phosphodiesterases (PDEs) contribute to the intracellular organisation of cyclic nucleotides signalling pathways in cardiac and vascular cells and will explore strategies to repair the alterations of these pathways in the context of hypertrophy/heart failure. Their project will focus on 4 research themes:

Compartmentation of cyclic nucleotide signalling. In this theme, team 2 intends:

1) to identify intranuclear and mitochondrial cAMP/PKA and/or cAMP/EPAC pathways in cardiac cells and determine their pathophysiological implication in heart failure;

2) to characterize the spatiotemporal control of EPAC activation by cAMP signals in cardiac and vascular smooth muscle cells;

3) to characterize the spatiotemporal control of cGMP signalling in vascular smooth muscle cells;

4) to identify the contribution of so far unstudied PDEs (PDE1, 8, 9 and 10) in regulating cardiovascular function;

5) to develop studies of cAMP signalling in intracellular compartments (nucleus and mitochondria) and nanoparticles immobilizing ligands of interest to investigate whether the localization of sarcolemmal proteins (L-type Ca^{2+} channels and β-adrenoceptors, in a first step) in T-tubular *versus* non T-tubular membrane, or caveolar *versus* non-caveolar membrane, impacts on their function and involves different intracellular molecular partners (depending on their localization). While the first objectives will be easy for this team to handle, the last one is more risky but very innovative and will benefit from a collaboration with chemists in the context of the LabEx LERMIT.

Regulation of the vascular contractile function by the cAMP pathway. The objectives of this theme, in line with previous studies, are:

1) to investigate the impact of the crosstalk between smooth muscle cells and endothelial cells on the function of the PDEs expressed in smooth muscle cells;

2) to investigate how PDEs regulate the downstream effectors of cAMP pathways with a focus on intracellular Ca^{2+} regulators and Ca^{2+}-activated K^+ channels, in collaboration with team 3;

3) to evaluate the respective contribution of EPAC and PKA in regulating the vascular tone. This theme will explore at the vascular level what the team has identified previously in the cardiac muscle. This is particularly important in the context of heart failure, a disease affecting the cardiovascular system as a whole.

Regulation of cardiac excitation-contraction coupling by the cAMP pathway. In this theme, team 2 intends to identify the nature of the PKA (I or II) and the proteins (mainly AKAP proteins) forming the PKA complexes which regulate the L-type Ca^{2+} current in cardiomyocytes. They also intend to identify the cellular signalling pathways leading to Ca^{2+} homeostasis perturbation and ventricular arrhythmias associated with PDE4 deficiency under β-adrenergic stimulation. This project, which will be performed in collaboration with team 3, is a logical follow-up of previous studies and is not expected to encounter major difficulties.

These three projects of basic, mechanistic science are expected to allow the identification of new putative therapeutic targets for treating heart failure and arrhythmias. The last one is dedicated to check in preclinical models whether PDE modulation could have a therapeutic application.

Preclinical studies and therapeutic applications. The objectives of this theme will be:

1) based on previous studies, to investigate whether cardiac overexpression of PDE4 or PDE2 in mouse could be beneficial in the context of heart failure and/or β-adrenergic stimulation;

2) to search for PDE activators, in collaboration with chemist partners from the LabEx LERMIT;

3) to investigate the role of PDEs in cardiac recovery from sympathetic stimulation in animal models;

4) to check whether the expression profile of β-adrenoceptor/cAMP/PDE pathway actors in lymphocytes could represent a biomarker of the severity of heart failure in patients.

These latter projects will be supervised by a University hospital practitioner (MCU-PH) who recently joined the team). The study in patients will be performed in collaboration with the *Département Hospitalo Universitaire* (DHU) TORINO (acronym for Thorax Innovation) in which RF is responsible for research activities.

Overall assessment of the program. The five-year research program of team 2 is in line with previous work and is a perfect balance between continuation of successful programs and development of new innovative projects. A special effort has been put on translational research, which was identified by the team as a weakness in their SWOT analysis. Team 2 has all the appropriate expertise and tools, as well as excellent funding, to make their overall project successful. The PIs of the different subprojects are clearly identified and well chosen.

Conclusion

- **Strengths and opportunities:**

- unique expertise and international recognition in cyclic nucleotide signalling;

- high funding and attractiveness;

- very Good technical and scientific environment (unit, IFR and LabEx);

- strong preliminary data, high expertise;

- development of translational and preclinical studies that should benefit from the LabEx LERMIT and the Ciblot platform;

- numerous established national and international collaborations.

- **Recommendations:**

Team 2 should consider developing new models of heart failure secondary to hypertension or metabolic disease, which are closer to the clinical situation, than the currently used models.

Team 3: Calcium Signaling and Cardiovascular Pathophysiology

Name of team leader: Ms Ana Maria GOMEZ GARCIA & Mr Jean-Pierre BENITAH

Workforce

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	3	3
N2: Permanent EPST or EPIC researchers and similar positions	2	2
N3: Other permanent staff (without research duties)		
N4: Other professors (PREM, ECC, etc.)		
N5: Other EPST or EPIC researchers (DREM, Postdoctoral students, visitors, etc.)	3	4
N6: Other contractual staff (without research duties)		1
TOTAL N1 to N6	**8**	**10**

Team workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	3	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit	7	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	4	5

• Detailed assessments

Assessment of scientific quality and outputs

Team 3, as it is now, was created in 2011 when Two PIs and part of their group group came from Montpellier. They were joined by a tenured faculty member of the School of Pharmacy from the Université Paris-Sud, already in site, in 2011, by a cardiologist, professor of physiology at the Faculty of Medicine of the Université Paris-Diderot in 2013, who had a long-term collaboration with them, and very recently by CNRS emeritus research director also MD. In September 2012, they recruited a new faculty member at the School of Pharmacy.

In the past 6 years (2008-2013), research projects of this new team were based on an excellent knowledge of intracellular calcium homeostasis and excitation-contraction coupling in cardiac myocytes. Studies were focused mainly on the regulation and function of the L-type Ca^{2+} current and the ryanodine receptor in pathophysiological

conditions (arrhythmias, heart failure, etc.) with a "molecule-to-whole animal" approach. A new topic focused on cardiotoxicity and cancer was initiated. The main results of the team are:

- the demonstration that the overexpression of FKBP12.6, a regulatory protein of the type 2 ryanodine receptor (RyR2), protects mice from Ca^{2+} - dependent arrhythmias occuring under β - adrenergic stimulation in basal conditions and heart failure;

- the demonstration that aldosterone or the overexpression of mineralocorticoid receptors (as observed in heart failure) induces a down-regulation of FKBP12.6;

- the identification of the arrhythmogenic mechanisms of a mutation of RyR2 identified in catecholaminergic polymorphic ventricular tachycardia (CPVT) by studying a knock-in mouse model;

- the demonstration that RyR2 hyperactivity (same CPVT mutation as above) induces a sinus node dysfunction in patients and mice;

- the demonstration that EPAC, a cAMP-activated exchange protein, can act as an activator of cardiac excitation-transcription coupling.

Team 3 shows a very good level of publication. From 2008 to 2013, the team has published 29 original articles and 13 review articles in peer reviewed referenced journals such as Circulation (4) Circulation Research, Cardiovascular Research, Journal of Molecular and Cellular Cardiology, cell calcium, etc, as well as 2 book chapters. Among the 42 peer reviewed articles, 22 originate from the team himself (5 with IF> 10; average IF = 7.66), 14 are collaborations with a major input of the team members (second and/or penultimate author) and 7 are collaborative publications with lower input. The large number of collaborative studies attests for the recognized expertise of the team. Those numbers only take into account the publications signed by current PIs.

The team also shows a good capacity to be funded: 5 international networks (3 as PI), 6 national public grants including 6 ANR grants (2 as PI) and 4 clinical grants (PHRC; 3 as PI) and a total of 8 university, LabEx, regional and private grants.

Assessment of the unit's academic reputation and appeal

The team is internationally recognized for its expertise on the role of intracellular calcium homeostasis in cardiac excitation-contraction coupling and arrhythmias.

Since 2008, the team members have been invited 42 times to give lectures in national and international meetings (including 2 Gordon Research Conferences) and seminars. They also organized 2 international symposia.

The team has been involved in 9 national and 5 international scientific project networks as partners (7) or leaders (7). They established 12 national and 16 international collaborations. They also participate in two international training networks including one EU-FP7 COST project.

One of the team leaders has been nominated as a Fellow of the European Society of Cardiology.

Members of the team are regularly reviewers for excellent journals. They are members of editorial boards of 4 different journals including 2 good specialty journals (Cardiovascular Research and the Journal of Molecular and Cellular Cardiology).

One PI applied as the European leader for a Leducq foundation transatlantic network of excellence which was pre-selected (10 best out of > 100) but not created.

These indicators clearly show that the team members have a very good national and international recognition.

Assessment of the unit's interaction with the social, economic and cultural environment

Since 2008, the team 3 has been involved in one industrial contract.

One MD of the team members has been the director of the Institut Claude Bernard (IFR 2, Université Paris-Diderot) from 2009 to 2012. Another member is highly involved in the LabEx LERMIT organization.

All team members are regularly involved in national and international steering and evaluation committees. The two team leaders have been elected in 3 different councils or executive boards of international scientific societies, including the Biophysical Society.

The team regularly welcomes middle school students and has been involved in popularization activities (Fête de la Science, 7 didactic articles for medical practitioners, interview).

Assessment of the unit's organisation and life

The team is well organized to deal with the project. It is an emerging team. Recruiting an engineer on a permanent position would stabilize the technological foundation of the team.

Assessment of the unit's involvement in training through research

Two PIs are tenured faculty members at the school of pharmacy of Université Paris-Sud and spend approximately 50 % of their time teaching pharmaceutical students. One PI is professor of cardiology at the faculty of medicine of the Université Paris-Diderot and coordinates the Master 2 "Biology, physiology and pharmacology of circulation and respiration" of Paris-Descartes, Paris-Sud, Paris-Diderot and Paris-Est Créteil Universities. One PI is coordinating a Master 2 teaching unit. The two team leaders are also involved in teaching.

Three PIs have the HDR (authorization to lead research) and train PhD candidates regularly. Since 2008, 8 students obtained their PhD. The team has also welcomed 1 foreign doctoral student (from Spain). Three PhD theses are ongoing. Seven post-docs have been trained and the team welcomed 2 visiting scientists from Cuba and Brazil.

The team is involved in 2 international training programs (one with Spain and one COST project, as team leader) and invites foreign students and post-docs through collaborative research networks.

Since 2008, the team has also trained 3 M2, 7 M1, 2 L3 students and 2 students from technical schools (BTS) for training.

Assessment of the strategy and the five-year plan

During the next 5-year period, the aim of team 3 project is to elucidate the roles and the mechanisms of Ca^{2+} flux alterations in the initiation of cardiac hypertrophy/heart failure and arrhythmias. The project will be focused on 5 themes:

• **Role of RyR in arrhythmia: Catecholaminergic Ventricular Polymorphic Tachycardia.** The aim of this project is to elucidate the mechanisms of ventricular arrhythmias in patients with CPVT and identify new therapeutic molecules. The studies will be focused on a RyR2 mutation identified in the N-terminal region of the channel, which is original compared to what has been/is done by concurrent teams. Two models will be used: a knock-in mouse model, already available, and cardiomyocytes differentiated from the patient induced pluripotent stem cells (iPSC), which will be obtained from patient's fibroblasts via a collaboration with clinicians from Spain and derived in cardiomyocytes by a US lab and/or a private company (Cellular Dynamics). In parallel, they will determine if FKBP 12.6 overexpression, by crossing CPVT mice with FKBP12.6 overexpressing mice (see above "assessment of scientific quality and outputs") can rescue the phenotype of CPVT mice. The search for new active drugs will be performed by the use of high throughput screening of chemical libraries in collaboration with Ciblot facility and the LabEx LERMIT. This project is a logical follow-up of previous ones and no particular difficulty can be anticipated except for the use of iPSC-derived cardiomyocytes, which is technically within the team's reach but time- and money-consuming. Although focused on a rare disease, CPVT, this project should shed light on arrhythmias occurring in common pathologies such as cardiac hypertrophy and heart failure, in which arrhythmias also depend on Ca^{2+} flux dysfunctions.

• **Role of RyR in arrhythmia: FKBP12.6.** As a follow-up of previous studies, team 3 will investigate more deeply the protective mechanisms of FKBP12.6 against catecholamine-dependent arrhythmias. The focus will put on the mechanism of the decreased sensitivity to catecholamines in mice overexpressing FKBP12.6 and on the role of stoechiometry between FKBP12.6 and FKBP12, a second RyR2 auxiliary protein belonging to the same family. This project is also quite straightforward.

• **Ca^{2+} signalling in heart failure: role of aldosterone.** In this theme, team 3 intends to:

1) identify the molecular mechanisms of mineralocorticoid receptor (MR)-dependent upregulation of Cav1.2 L-type Ca^{2+} channel, previously shown by the team. Based on preliminary results, the team will use High Throughput Microscopy and ChIP-seq on cultured neonatal cardiomyocytes to determine if Cav1.2 transcription is directly regulated by MR through binding on glucocorticoid response elements. A mouse model expressing luciferase reporter gene under control of Cav1.2 gene promoter region will then be investigated using bioluminescence imaging and classical methods of in vivo cardiac function evaluation including echocardiography;

2) investigate whether Store-Operated Channels such as TRPC and Orai are MR target genes in cardiomyocytes;

3) identify new target genes of aldosterone using ChIP-seq on normal and pathological cardiomyocytes.

Although this project implies new concepts and techniques for team 3 members, the risk is limited by the established collaboration with team 1 and M. Lombès, from the Inserm unit 693.

• **Role of EPAC in enhancing Ca^{2+} entry. Are TRPC involved?** In line with previous work about the role of EPAC in cardiac Ca^{2+} signalling, this emerging program is aimed at identifying the channels involved in Ca^{2+} entry and excitation-transcription coupling. Since EPAC poorly affects the L-type Ca^{2+} channel, the team hypothesis is that non-voltage dependent Ca^{2+} permeant channels, such as TRPC, Stim and Orai channels, which cardiac functions are poorly understood, would be involved. Although there is no preliminary data in favour of this hypothesis, based on the properties of these channels, it seems worth developing the project, which will benefit from the expertise of Ms Jessica SABOURIN in the subject.

• **Heart failure induced by anticancer therapy.** The objective of this new program, headed by Mr Eric MOREL, is to elucidate the signalling pathways involved in anticancer radio- and chemotherapy cardiotoxicity in order to identify therapeutic targets. Part of this program is included in the T1-3 "Target" project of LERMIT LabEx. The first objective is focused on the kinetics of cardiotoxicity and the role of EPAC 1 and 2 in its development by using cultured cardiomyocytes and mouse models. The second objective is aimed at identifying the actors of the signalling pathways involved in radiotherapy- and chemotherapy-induced toxicity, with a focus on the role of Ca^{2+} homeostasis regulators, of small G proteins and Guanine nucleotides Exchange Factors (GEFs, including EPAC), well-described fibrosis leading pathways and the implication of miRNAs. This new program, which deals with an important public health problem, appears quite ambitious, especially since Mr Eric MOREL is only part-time in the lab. It would probably benefit by being more focused on Ca^{2+} homeostasis, EPAC and small G-proteins pathways.

• **Overall assessment of the program.** Team 3 five-year research program is consistent with previous work. It is well-balanced between ongoing projects and more risky new projects (TRPC, regulation of L-type Ca^{2+} channel expression, etc.), and between fundamental and translational research. The team possesses most of the expertise and equipment to perform their studies, with the exception of the study on gene expression regulation which will be performed with an external partner. The development of a new project on heart failure induced by anti-cancer therapy is ambitious but will be headed by an experienced scientist.

The overall project seems feasible based on the expertise and the excellent level of funding of the team. The project is well structured with well-identified objectives, PIs and funding.

Conclusion

- **Strengths and opportunities:**

- excellent funding and good attractiveness;

- very good technical and scientific environment (Ciblot platform and LabEx LERMIT);

- strong preliminary work, high expertise in calcium signalling and calcium imaging;

- numerous established national and international collaborations;

- very good translational activity consistent with an MD joining the team.

- **Weaknesses and threats:**

The future director needs to ensure not to be overcome by the administrative work.

- **Recommendations:**

Team 3 should seek recruiting 1 engineer or technician on a permanent position.

Considering the quality of the team and projects it is worth to try to join an international network (Leducq foundation or Horizon 2020).

5 • Conduct of the visit

Visit date:

Start: Wednesday February 5th 2014 at 8:30 am

End: Wednesday February 5th 2014 at 5:30 pm

Visit site:

Institution: Faculty of Pharmacy, Université Paris-Sud

Address: 5 Rue Jean-Baptiste Clément

92296 Châtenay-Malabry, France

Specific points to be mentioned:

The following people also attended the visit:

- Mr Raymond BAZIN (AVIESAN);

- Mr Tahar KAABACHE (Représentant ITA, CSS4 INSERM).

6 • Supervising bodies' general comments

UNIVERSITÉ PARIS SUD

Comprendre le monde, construire l'avenir®

Le Président de l'Université Paris-Sud

à

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

Orsay, le 7 mai 2014

N/Réf. : 127/14/JB/LM/AL

Objet : Rapport d'évaluation d'unité de recherche
N° S2PUR150007984

Monsieur le Directeur,

Vous m'avez transmis le 8 avril dernier, le rapport d'évaluation de l'unité de recherche «SIGNALISATION ET PHYSIOPATHOLOGIE CARDIOVASCULAIRE » – N° S2PUR150007984, 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.

Vous trouverez en annexe les éléments de réponse de Madame Ana Gomez-Garcia, future directrice de l'unité de recherche.

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

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Dr Ana Maria Gomez

Prof. Pierre GLAUDES
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Châtenay-Malabry, le 29 avril 2014

Réf. : E2015-EV-09110C-S2PUR150007984-004902-RT_GomezGarcia

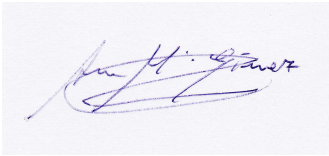
Dear Professor Glaudes,

We would like to thank the AERES and its representatives for selecting internationally renowned experts perfectly competent to judge our work.

We also thank the President and all expert committee members for their constructive interaction with us during the evaluation procedure, and the elaboration of a very detailed and well-argued report. We are very pleased to read that your opinion on our activity and project is very positive, acknowledging that the research of all three complementary teams has led to major results, that our projects are original and very well balanced, and concluding that we form an excellent and attractive unit. This rapport encourages us to pursue our objectives for the next period, what we will do following your valuable suggestions and recommendations.

We also thank the representatives of our supervising institutions for their presence during the visit of the evaluation committee and for their precious support.

Sincerely,



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