Research evaluation

EVALUATION REPORT OF THE UNIT

CARPAT - Signalisation et physiopathologie cardiovasculaire

UNDER THE SUPERVISION OF THE FOLLOWING ESTABLISHMENTS AND ORGANISMS:

Université Paris - Saclay,
Institut national de la santé et de la recherche médicale - Inserm

EVALUATION CAMPAIGN 2024-2025
GROUP E

Rapport publié le 27/02/2025

High Council for evaluation of research and hihter education

In the name of the expert committee :

Thierry Pedrazzini, chairman of the committee

For the Hcéres :

Stéphane Le Bouler, acting president

In accordance with articles R. 114-15 and R. 114-10 of the Research Code, the evaluation reports drawn up by the expert committees are signed by the chairmen of these committees and countersigned by the president of Hcéres.

To make the document easier to read, the names used in this report to designate functions, professions or responsibilities (expert, researcher, teacher-researcher, professor, lecturer, engineer, technician, director, doctoral student, etc.) are used in a generic sense and have a neutral value.

This report is the result of the unit's evaluation by the expert committee, the composition of which is specified below. The appreciations it contains are the expression of the independent and collegial deliberation of this committee. The numbers in this report are the certified exact data extracted from the deposited files by the supervising body on behalf of the unit.

MEMBERS OF THE EXPERT COMMITTEE

Chairperson:	Mr Thierry Pedrazzini, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland
Experts:	Ms Giuseppina Caligiuri, Institut national de la santé et de la recherche médicale – Inserm, Paris (representative of the CSS Inserm) Mr Laurent Monassier, université de Strasbourg (representative of the CNU) Mr Benjamin Grenier-Boley, Institut Pasteur de Lille (representative of the supporting personnel) Ms Jolanda Van Der Velden, Amsterdam UMC, the Netherlands

HCÉRES REPRESENTATIVE

Ms Florence Pinet

REPRESENTATIVES OF SUPERVISING INSTITUTIONS AND BODIES

Mr Raymond Bazin, Inserm
Mr Philippe Arhets, Inserm
Mr Elias Fattal, Université Paris - Saclay
Ms Anne Monsoro-Burq, Université Paris - Saclay

CHARACTERISATION OF THE UNIT

- Name: Signalisation et physiopathologie cardiovasculaire
- Acronym: Carpat
- Label and number: UMR-S 1180
- Composition of the executive team: Director: Ms AM Gomez, the past-director: Mr R Fischmeister and the co-directors of each team: Mr Mathias Mericskay, Ms Anne Garnier, Mr Grégoire Vandecasteele, Ms Véronique Leblais, and Mr Jean-Pierre Benitah

SCIENTIFIC PANELS OF THE UNIT

SVE Sciences du vivant et environnement
SVE6 Physiologie et physiopathologie humaine, vieillissement

THEMES OF THE UNIT

The "Signalling and Cardiovascular Pathophysiology" unit (Carpat) (UMR-S 1180, Inserm/University Paris-Saclay) is a research unit composed of three teams which aims to determine alterations in the context of heart failure, and ways to prevent or rescue the heart, and to identify the mechanisms involved in normal rhythm and arrhythmia. The unit approach involves the characterisation of cardiomyocyte's functions such as electrical activity, contractility, excitation-contraction coupling, and energetics… Members study i) the perturbation of energy metabolism and signalling in heart failure (team1); ii) the cyclic nucleotide signalling in normal heart and vessels and how this is involved in the progression of heart failure (team2); iii) the dysregulation of Ca2+ signals impacts the pathogenesis of heart failure and arrhythmias (team3).

HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

The Carpat unit (Director: Ms AM. Gómez) was created in 2015 from the former unit UMR-S 769 "Signalling and Cardiac Pathophysiology" (Director: Mr R. Fischmeister) and was renewed in 2020. The unit was initially located at the Pharmaceutical School of University Paris-Sud, in Châtenay-Malabry until August 2022 and are now located at the Faculty of Pharmacy of the University Paris-Saclay, in Orsay. The three teams of the unit share around 1600 m² of laboratory and office spaces in a new research building.

RESEARCH ENVIRONMENT OF THE UNIT

Since 2022, the unit is relocated in a new research building in the dynamic campus of Orsay. This allows the unit to be a member of the UMS-IPSIT (Paris-Saclay Institute of Therapeutics Innovation) which brings together ten technology platforms and eleven laboratories with 25 research teams where the unit benefits from expertise and collaboration. Of note, Ms Anne Garnier, co-leader of team 1, is the scientific director of the UMS-IPSIT and Mr G. Pidoux, future co-leader of team 1, is the scientific director of the imaging core facility MIPSIT. .
The unit owns an imaging platform consisting of a confocal microscopy, two FRET systems, one Ionoptix and one epifluorescence microscope. The unit is also equipped with electrophysiological equipment with four patch-clamp set-ups, one microelectrode and one lipid bilayer system. The laboratory space of the unit includes two L2 and one L1 laboratories. The unit has also access to the animal core facility where they have located their ECG telemetry equipment as well as a LAZRX (VisualSonics), an high resolution echocardiography and photoacoustic equipment which was partially funded by the unitThe unit was a founding member of the Laboratory of Excellence Lermit, led by Mr R. Fischmeister for the period 2011-2022 which included around fifteen laboratories to develop original translational research on the identification of new therapeutic targets including cardiovascular diseases. Since 2020, the unit is also part of the "Paris-Saclay Institute for Health and Innovative Therapeutics" (Healthi), an interdisciplinary institute funded by the University Paris-Saclay, to facilitate research of therapeutics innovation (e.g. target identification, drug design, diagnostic, imaging tools, etc.) by leading the axis 5 "Cardiovascular, lungs and haemostasis".

UNIT WORKFORCE: in physical persons at 31/12/2023

Catégories de personnel	Effectifs
Professeurs et assimilés	5
Maîtres de conférences et assimilés	10
Directeurs de recherche et assimilés	4
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	7
Sous-total personnels permanents en activité	**28**
Enseignants-chercheurs et chercheurs non permanents et assimilés	7
Personnels d'appui non permanents	2
Post-doctorants	4
Doctorants	13
Sous-total personnels non permanents en activité	**26**
Total personnels	**54**

DISTRIBUTION OF THE UNIT'S PERMANENTS BY EMPLOYER: in physical persons at 31/12/2023. Non-tutorship employers are grouped under the heading "others".

Nom de l'employeur	EC	C	PAR
U PARIS SACLAY	12	0	3
INSERM	0	6	4
AUTRES	3	0	0
Total personnels	**15**	**6**	**7**

GLOBAL ASSESSMENT

Overall, the unit enjoys an excellent reputation within the cardiovascular research community. Its scientific program is coherent, compelling and globally excellent and it integrates research from all three teams, making it an attractive destination for researchers, students (29 PhD defenses), postdocs, and visiting professors, coming from various countries (US, Canada, Brazil, Chile, Morroco, China, Spain, Lebanon, Germany…). Funding bodies are highly supportive, and the unit benefits from a robust budget, thanks to the teams' ability to secure external grants with a budget over 1 million Euros per year over the past three-four years from NIH, Leducq foundation, ERA-CVD, 6 ANR) despite no ERC grants, or major European grants. Notably, the Unit has also organised prestigious international conferences (Gordon, ISHR-ES Annual Meetings, World congress of ISHR) and members of the unit were invited for numerous international conferences (ESC, Gordon, ISHR…). As a result, the unit's scientific output is outstanding.
The unit's scientific production is outstanding within its field of research. with 222 papers during the evaluation period, including 159 original articles (63 with members listed as first or last authors), 63 reviews, editorials, and seven book chapters. Some important papers have been published in renowned journals such as Circulation, Circulation Research, Cardiovascular Research, and eLife. The unit has made significant contributions to understanding cardiovascular signalling mechanisms in cardiomyocytes and arterial smooth muscle cells, cell metabolism and energetics, cyclic nucleotides and phosphodiesterases, and calcium channels. The scientific production is well distributed among the three Teams and fifteen articles involve at least two teams. Publications appear in specialised journals and do not include major articles in journals with a broader readership.Areas for improvement include a more clearly defined set of objectives for the unit, particularly with respect to identifying the primary target pathology. Additionally, while the unit emphasizes the importance of translational science, this aspect is not fully realised. The unit is positioned in the field of basic pathophysiology and the study of preclinical models. Strengthening ties with clinical partners and enhancing the protection and valorisation of intellectual property will be essential to achieving this goal. The unit's operations could also benefit from improved communication, both within and between teams. Redefining the role of the scientific committee could provide a valuable platform for prioritising research programs within each team, ensuring better alignment with the unit's overarching objectives. Along these lines, applying for ambitious European calls, such as ERC grants, should be considered to elevate the unit to the next level of excellence.

DETAILED EVALUATION OF THE UNIT

A - CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

Recommendations on scientific production and activities: The unit should encourage more international networking – international PhD / post-docs, grants. They should continue to open positions for visiting professors on regular basis.

Response

During the past term, the unit hired twenty international PhD. students and post-docs (two of them in international co-direction; Brazil and Lebanon) in short-term internships funded by international organisations such as EMBO, European grants, Ecos, European Foundation for diabetes Studies, Eiffel Program of Excellence from Campus France, Mexico Conacyt program, China Scholarship Council. These students came thanks to our collaborations with different countries: Spain, Jamaica, Chile, Lebanon, Algeria, Morocco, Israel, Germany, Mali, Mexico, Russia, UK. The unit welcomed 7 visiting professors (4 USA, 1 Brazil, 1 Lebanon and 1 Cuba).

Recommendations on the unit's organisation and life: The unit should organize translational seminars and strengthen the interaction with clinical research in the unit's organisation.

Response

The unit has strengthened its collaborations with the clinicians of Marie Lannelongue Hospital, submitting joint grant applications, and developing three projects (pulmonary hypertension, cardiac graft preservation). The unit has ongoing collaboration with cardiologists in Spain, resulting from common publication mixing clinical and experimental data. The unit recently integrated in the laboratory two MCU-PH (assistant professors-hospital practitioners, one in KB Hospital; one in George Pompidou Hospital), and started translational projects.

Recommend actions on scientific strategy and projects: The unit should strengthen international networks and innovation. The excellent research activity of the labs should encourage it to explore novel directions and propose some more risky projects.

Response
The unit obtained four international grants (NIH-France 2020 R01, Germany DFG-France ANR, Leducq Transatlantic network, and ERA-Net CVD). The unit participated in two COST European action networks, and to the European-funded network Rise from the H2020 call.
In terms of new projects, the unit has implemented Hipsc-derived cardiomyocytes in the lab.

Comments
International networking activities:
The unit has strengthened its connections with international institutions, leading to the launch of research projects involving various European institutions. This effort has successfully attracted funding. The majority of the non-permanent members come from abroad. Overall, the unit has enhanced its international visibility and attractiveness.

Translational aspects:
The unit has initiated some projects with the Marie Lannelongue Hospital and mentioned recent efforts to improve this area of research. However, further improvements could be made to facilitate the clinical application of research findings. Dedicated translational programs should be established.

B - EVALUATION AREAS

Guidelines for all areas of evaluation (1, 2, 3 and 4): Considering the references defined in the unit's evaluation guidelines, the committee ensures that a distinction is made on the outstanding elements for strengths or weaknesses. Each point is documented by observable facts including the elements from the portfolio. The committee assesses if the unit's results are consistent with its activity profile.

EVALUATION AREA 1: PROFILE, RESOURCES AND ORGANISATION OF THE UNIT

Assessment on the scientific objectives of the unit

The scientific program is coherent and globally excellent and it integrates research from all three teams. However, the unit's profile, overarching expertise, primary focus, and target pathology need clearer definition. While the unit identifies itself as a basic, preclinical, and translational research center, the translational aspect is not strongly evident. If pursuing translational research is indeed a primary objective, the unit should focus on establishing the necessary conditions for its success. The objectives of each team are well-defined, but certain research lines would benefit from better alignment with the unit's main goals.

Assessment on the unit's resources

The Unit has done an excellent job attracting funding with a budget over 1 million Euros per year over the past three to four years, and the number of personnel appears adequate, but the situation could be improved by applying to more ambitious calls (ERC grants, European grants).
However, certain areas of expertise are not fully covered. Additional support for animal science would be beneficial, and the Unit should also consider hiring a professional bioinformatician to strengthen its capabilities.

Assessment on the functioning of the unit

The Unit's overall functioning is very good. However, there is room for improvement in communication across all categories of personnel and also both inter and intra-teams. The role of the scientific committee in the Unit's operations is not entirely clear. Its involvement in fostering inter-team projects and prioritising research lines should be better defined.

1/ The unit has set itself relevant scientific objectives.

Strengths and possibilities linked to the context

The research focuses on investigating the main functions of cardiomyocytes: electrical activity, excitation-contraction coupling, contractility, and energetics. The unit is organised into three teams: Team 1 studies disruptions in energy metabolism and signalling in heart failure. Team 2 explores the organisation of cyclic nucleotide signalling in both healthy and diseased heart and blood vessels. Team 3 investigates the dysregulation of calcium signals in heart failure and arrhythmias. The unit's stated objectives are: to identify alterations in heart failure (energetics, signalling, etc.) and discover ways to prevent heart failure or potentially reverse it; and: To elucidate the mechanisms underlying normal heart rhythm and arrhythmias. The research projects focus on topics such as NAD and sirtuins, Ca2+ channels, and phosphodiesterases, particularly in the context of Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT) and sudden death. Overall, these objectives form a coherent program that integrates research from all three teams.

Weaknesses and risks linked to the context

The unit likely lacks ambitious research programs based on potentially high-risk, high-yield propositions, which could help attract funding and enhance the unit's reputation.

2/ The unit has resources that are suited to its activity profile and research environment and mobilises them.

Strengths and possibilities linked to the context

The unit declares a budget over 1 million Euros per year over the past three-four years. The University provides a recurrent support of 61,000 euros a year. On top of that, it offers other support on a competitive basis . The majority of the budget comes therefore from grants (e.g., ANR, Leducq, French Society of Cardiology). Additionally, the unit receives a recurrent support from Inserm, which contributes to 173,000 Euros a year (as set in 2020). For equipment and costly investments, the requests are presented and justified at a general assembly meeting in January. The unit has successfully applied to different large equipment calls. The echography apparatus Vevo LAZRX, Visual Sonics was obtained thanks to a regional Sesame grant of 350,000 Euros, a Mutualised Research Equipment grant of the UPSaclay (71,000 Euros), and exceptional funds from INSERM (50,000 Euros).

Weaknesses and risks linked to the context

Overall, the unit has limited European grants and no ERC/EU grants.

3/ The unit's practices comply with the rules and directives laid down by its supervisory bodies in terms of human resources management, safety, environment, ethical protocols and protection of data and scientific heritage.

Strengths and possibilities linked to the context

The executive team, which consists of the director, the past director, and the co-directors of each team, meets once a month. This team handles confidential human resources issues, the integration of new unit members, and other key concerns, which will be presented in the lab council to make decisions . The laboratory council, composed of all unit members, meets every Monday morning to make announcements and decisions, such as updates from supervising institutions, human resources regulations, and take decisions on lab strategy and investments on a consensus or voting basis, as well as discuss lab organisation.. At least twice a year, the council focuses on budget discussions. The unit holds weekly scientific meetings for all members. The unit has implemented Inserm's policies on research misconduct, in line with the European Code of Conduct for Research Integrity, promoting scientific values such as objectivity and reproducibility. Data security is managed by a designated person responsible for computers, servers, and IT infrastructure. In accordance with Inserm guidelines and the laboratory's welcome booklet for new members, the unit enforces a health and safety policy to prevent risks associated with laboratory activities. A business continuity plan is in place, listing personnel available for emergencies. One lab member is a delegate for sustainable development, with initiatives such as selective waste disposal already implemented. All animal experiments comply with Directive 2010/63/EU of the European Parliament, dated September 22, 2010, which protects animals used for scientific purposes, as well as with French

institutions' animal care guidelines. The unit follows the 4 Rs principles: Reduction, Refinement, Replacement, and Reproducibility. The unit promotes gender equality, with a female scientist as the director. There is a perfect gender balance in team leadership (50% women), and women make up 45% of the permanent staff and 53% of all lab members.

Part-time positions are available upon request to support a healthy work-life balance.

Lab members have completed a course organised by UPSaclay on sexual harassment and sexist behaviour awareness. The unit has an anonymous reporting system for any issues. One individual serves as the Inserm delegate for gender equality and parity, working to combat discrimination. Another lab member focuses on student well-being within the doctoral school to prevent and address psychosocial risks. The lab director conducts annual reviews of all personnel to identify potential problems.

Weaknesses and risks linked to the context

The communication within the unit is insufficient, both inter and intra-teams.
All written communications should be in both French and English.
People responsible for equipment maintenance and cleaning are not clearly identified to ensure smooth functioning of the technical labs.

EVALUATION AREA 2: ATTRACTIVENESS

Assessment on the attractiveness of the unit

The Unit has an excellent scientific reputation and is highly regarded in the cardiovascular field for its expertise in signalling and metabolism. It attracts a wide range of students (29 PhD defences), postdocs, and visiting professors, and has been very successful in securing funding from various agencies for a total amount of 7,84M€. The unit has not reported any ERC grants, or major European grants. Notably, the Unit has also organised prestigious international conferences (Gordon).

1/ The unit has an attractive scientific reputation and is part of the European research area.

2/ The unit is attractive because for the quality of its staff support policy.

3/ The unit is attractive through its success in competitive calls for projects.

4/ The unit is attractive for the quality of its major equipment and technical skills.

Strengths and possibilities linked to the context for the four references above

1. The unit is recognised for its expertise in cardiac cellular metabolism, cyclic nucleotide signaling, electrophysiology, and intracellular calcium handling. Members are active in French associations, such as the Société Française de Cardiologie, GRRC, Meetochondrie, and the Société Française de Pharmacologie and Toxicologie, as well as in European associations (ESC) and international organisations (ISHR), sometimes serving as committee members. Unit members also act as experts on Inserm and CNRS committees. The unit benefits from international recognition, demonstrated by numerous collaborations with research groups abroad and invitations to present at international conferences (e.g., ESC, ISHR, Gordon Conferences (n=72)). Additionally, members contribute to organising international conferences (n=28). Several team members have been honored by their peers, receiving awards and recognition at various conferences.
2. The unit focuses on creating a friendly and supportive environment. The unit actively recruits new members, especially non-permanent ones. PhD students get support from the doctoral school or various grants. The unit welcome visiting scientists from abroad (US, Canada, Brazil, Chile, Morroco, China, Spain, Lebanon, German…). The unit encourages the promotion of all its members. The director, in particular, makes sure that the technical staff gets recognition and supports their advancement both within Inserm and the university. The unit also provides funding to help members attend scientific conferences.

3. The unit encourages its members to apply for external funding and has been quite successful in this area. It has secured nine ANR grants (8 as PI), along with other grants through international collaborations in Europe (ERA-CV-net, bilateral German DFG) and America (NIH, Transatlantic Network Leducq), nearly all with a member of the unit as PI.
4. The unit is recognised for its expertise in imaging. It has developed a platform that includes one confocal microscope, two FRET systems, one Ionoptix system, and one epifluorescence microscope. The unit is also skilled in electrophysiology and benefits from a platform in this area of research, which consists of four patch-clamp setups, one microelectrode, and one lipid bilayer system. A laboratory is dedicated to organ physiology, allowing for the assessment of vessel contractility, whole-heart ECG, pressure-volume curves, and electrical mapping. Team 1 focuses on measuring mitochondrial respiration and fiber contractility. Animal experiments utilize one ECG telemetry system and one high-resolution echocardiography system with photoacoustic equipment. Overall, the unit can provide all the major techniques needed for its research.

Weaknesses and risks linked to the context for the four references above

1. Many recognitions have been awarded to the current director, Ms Anna-Maria Gómez, or the former director. While this does not diminish their achievements, other team members are not included for their visibility and profiling activities.
2. It is unclear how the unit is working to attract permanent members, create new teams, and expand its critical mass of scientists.
3. The unit has not reported any ERC grants, or major European grants.
4. In the past, expensive equipment was acquired through pooled financial resources, but changes in institutional policy may make it harder to obtain such equipment in the future.

EVALUATION AREA 3: SCIENTIFIC PRODUCTION

Assessment on the scientific production of the unit

The unit's scientific production is outstanding within its field of research with 222 papers during the evaluation period, including 159 original articles (63 with members listed as first or last authors), 63 reviews, editorials, and seven book chapters. Some important papers have been published in renowned journals such as Circulation, Circulation Research, Cardiovascular Research, and eLife. The scientific production is well distributed among the three Teams and fifteen articles involve at least two teams. Publications appear in specialised journals and do not include major articles in journals with a broader readership. Publications in generalist journals are collaborative work (Molecular Metabolism, Science Adv, Embo Mol Med…)

1/ The scientific production of the unit meets quality criteria.

2/ The unit's scientific production is proportionate to its research potential and properly shared out between its personnel.

3/ The scientific production of the unit complies with the principles of research integrity, ethics and open science. It complies with the directives applicable in this field.

Strengths and possibilities linked to the context for the three references above

The unit's members have published 222 papers during the evaluation period, including 159 original articles (63 with members listed as first or last authors), 63 reviews, editorials, and seven book chapters. The unit successfully published as example 1) on nicotinamide riboside (NR) kinase 2 as new regulator of NAD metabolism and they showed benefit of NR supplementation in a model of dilated cardiomyopathy with >200 citations (published in Circulation); 2) new insight in mobilisation by b2-AR of a new perinuclear cAMP/PKA microdomain to regulate gene expression in cardiomyocytes (Cardiovasc Res) and 3) the role of Epac/Ca2+ in the context of diabetes (Cardiovasc Res)and of cardio-oncology (eLife).
1.Some important papers have been published in renowned journals such as Circulation, Circulation Research, Cardiovascular Research, and eLife.
2. The scientific production is well distributed among the three Teams and fifteen articles involve at least two teams.

3. Overall, the unit complies with good scientific practices. Scientists are required to document their experiments in notebooks, which are properly archived to ensure scientific quality and integrity. The Inserm electronic version of the notebook (Labguru) is also available to validate protocols, save them, and share them among all lab members. Raw data and their analysis are discussed in face-to-face meetings with supervisors and presented during internal meetings. Principal investigators are responsible for their more junior collaborators. The publication policy is based on the authors' involvement in the research to determine authorship. Each author must make significant contributions. All publications are posted on the Inserm Portal of the French National Open Repository HAL, allowing for free access. Papers are usually published open access. Human samples are anonymised and obtained with patient approval after the protocol has been reviewed by the relevant ethical committees. All animal experiments are submitted to the local ethical committee and to the "ministère de l'Enseignement supérieur et de la Recherche" for approval.

Weaknesses and risks linked to the context for the three references above

1. Publications appear in specialised journals and do not include major articles in journals with a broader readership. The unit's scientific output of original papers, in which members are listed as first or last authors, is excellent, but the number of papers is somewhat limited.

EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

Assessment on the inclusion of the unit's research in society

The Unit is very good in outreach efforts and fostering relationships with industry (one Cifre contract, 2 patents). However, it is less effective in capitalising on its intellectual property, forming startups, or similar initiatives. At this stage, the Unit has not yet achieved a level where its research generates significant social impact.

1/ The unit stands out for the quality and the amount of its interactions with the non-academic world.

2/ The unit develops products for the cultural, economic and social world.

3/ The unit shares its knowledge with the general public and takes part in debates in society.

Strengths and possibilities linked to the context for the three references above

1. The unit has organised several courses, including an international course for the Research and Innovation Staff Exchange (Rise) program and an educational course titled "Electrophysiology for Clinicians" for the European Heart Rhythm Association. The unit has also hosted events for stakeholders and organised a summer school. Additionally, it is actively engaged with the European University Alliance for Global Health (EUGLOH). The unit has secured industry partnerships, including a Cifre contract with Sanofi and contracts with G-LIFE, Pfizer, Mironid-UK, and Cydan-USA.
2. The unit participates in special events, such as the "Day of Women and Girls in Research," the Science Week, and "La Fête de la Science," organised by UPSaclay.
Team 1 has filed two patents on the treatment of cardiomyopathies by nicotinamide riboside.
3. The unit has a website that provides information on its activities, conferences, and publications. The various teams are active on social media platforms. The unit contributes to knowledge dissemination and interacts with lay audiences, including the general public and schools, to promote scientific culture. Each year, the unit welcomes 3rd-grade students (ages 13-15) for a one-week internship to expose them to science. The unit has participated with Inserm in organising the "Destination Labo" program to promote research in high schools. Additionally, the unit co-organizes an annual public event on cardiology research as part of the "Fête de la Science." It also contributes articles targeted at the scientific community in the newsletter Life Sciences of the University of Paris-Saclay.

Weaknesses and risks linked to the context for the three references above

1. The unit does not report collaborations with patient associations.

2. The unit appears somewhat hesitant in protecting its breakthroughs through patenting, and the potential creation of startups, which could foster job creation. It is also unclear how the unit ensures long-term sustainability and public trust. While these are not major issues, they should be given more consideration in the future.

ANALYSIS OF THE UNIT'S TRAJECTORY

Long-term scientific history and objectives
In the next five years, Director Ms A.M. Gómez plans to step down from leadership after two terms and is suggesting Mr Mericskay as the new director, with her support as deputy. Each team has also promoted a younger co-leader to ensure a smooth transition to the next generation while still benefiting from experienced guidance. The reorganisation was discussed in lab meetings and approved through ballots to align with the unit's ethical values and commitment to research and training. Additionally, there is a promising opportunity for recruiting a new researcher in the unit through the Junior Professor Chair tenure-track program, a government initiative for which the unit was selected among the four chair programs allocated to Paris-Saclay University in 2024. This recruitment will take place in 2024 and will strengthen the unit's research activities in the next term. Overall, the unit's management is well-established.

Actual position of the unit at the national and international level
The unit is recognised nationally and internationally due to the efforts of its leaders and ongoing participation in scientific organisations. Key figures include Ms A.M. Gómez, who served on the Inserm expert evaluation committee and chaired the ESC Working Group on Cardiac Cellular Electrophysiology, and Mr Mericskay, who joined the committee in 2022. The unit is also involved in the COST Action "EU-Me-Heart" network, with over 250 participants from more than 40 countries. Several members have received prestigious awards, and the teams maintain a broad network of international collaborators and participate in national consortia funded by ANR.

Unit Scientific Projection
The unit plans to continue its research aimed at elucidating heart failure (HF) mechanisms, with a particular emphasis on gender issues. It will focus on various forms of heart failure, including heart failure with reduced ejection fraction (Hfref) and heart failure with preserved ejection fraction (Hfpef), while exploring the physiological and cellular regulations critical to contractile function. Additionally, the unit aims to leverage the interdisciplinary environment at Paris-Saclay to collaborate with experts in medical chemistry and multi-omics analyses, enhancing our understanding of HF and cardiac rhythm disorders. Overall, this makes a coherent research program.

Team 1 will focus on enhancing heart failure treatment through vitamins that stimulate mitochondrial metabolism. They will investigate these treatments in both Hfref and Hfpef models. The team will also explore NAD metabolism and signalling across different heart failure models, taking sex differences into account. New research areas will emerge, such as studying the role of AKAP signalling in Hipsc cardiomyocytes.

Team 2 aims to unravel the cyclic nucleotide pathways in cardiomyocytes and vascular cells by utilising modified agonists and antagonists to differentiate between T-tubular and sarcolemmal β-adrenergic receptors. Their research will investigate the role of PKA type I in cardiac functions and remodelling, as well as in the pathophysiology of hereditary cardiac myxomas. The vascular aspect will focus on cAMP signalling in Hfpef and the role of SERCA3 in calcium homeostasis. They will also pursue translational studies on phosphodiesterase-based gene therapy for Hfref, leveraging Hipsc cardiomyocyte models.

Team 3 will examine the role of calcium flux in maintaining normal heart rhythm and its disruption in various pathologies, including Hfref and drug toxicity. They will study ionic channels and their regulation by Epac, focusing on the implications of calcium alterations in cardiac contractility and arrhythmias. The team aims to explore genetic arrhythmias and personalize treatment using Hipsc cardiomyocyte models. Their ongoing research on the circadian regulation of L-type calcium channels will help elucidate the molecular mechanisms underlying daily heart function and its disruption in disease states.

Emergence of new themes
Collaborative efforts and projects within the unit: creation of transversal working groups
The teams share common goals in studying cyclic nucleotide signalling, calcium flux, and mitochondrial function in the context of Hfpef. Recent rodent models, such as the high-fat diet combined with L-Name and others, aim to mimic Hfpef associated with metabolic syndrome. New mouse models without obesity phenotypes are emerging, prompting each team to develop relevant rodent models tailored to their specific questions. To enhance collaboration, they will share biological materials from pilot studies, coordinate experiments through a transversal working group, and establish standardised cardiac function readouts for a common database to facilitate future research.

The development of Hipsc cardiomyocytes offers promising opportunities. Advances in 3D culture systems and organoids aim to enhance the maturation of Hipsc cardiomyocytes toward adult cardiomyocytes, making these models more accessible to non-expert labs. The unit is fostering collaboration with renowned experts and forming a transversal working group to optimize production, sharing differentiation schedules and analyses, which will improve understanding of both in vivo and in vitro models and should lead to collaborative

publications. One joint project aims to decipher the impact of anthracyclines on Hipsc cardiomyocytes from patients with varying sensitivities to the cardiotoxic effects of anticancer drug therapies.

Possibilities offered by the environment
The unit is now situated in a new research building on the Paris-Saclay University campus, which offers a rich scientific environment. This location enhances collaboration opportunities, particularly with the Institut Galien Paris-Saclay on nanodrug design. The unit is part of the Healthi consortium, which includes 58 laboratories and enables access to funding. The unit benefits also from easy access to technological platforms like UMS-IPSIT and other facilities for high-throughput metabolomics (CEA Institut Joliot) and advanced microscopy (Ecole Normale Paris-Saclay; CNRS campus), and collaborates with a network of bioinformaticians to optimize data processing workflows.

Partnership strategy with the academic world and the socio-economic and cultural world
Internationally, the unit aims to establish international training networks, such as European Doctoral Networks through Marie Skłodowska-Curie Actions, leveraging connections with collaborators and the Graduate School HEADS. To enhance interactions with the biotech and pharmaceutical sectors, they will work with the Paris-Saclay SATT to protect intellectual property and promote their research. Additionally, the laboratory will engage the public through initiatives like the "Fête de la Science," welcoming visitors, families, and students to explore science in an accessible and enjoyable format.
Coherence of unit research strategy with its resources and organisation
Over the next five years, the unit will have at least 29 permanent staff members, including 6 full-time research positions and 14 teaching researchers, with no current investigators reaching retirement age during this period. The unit plans to recruit new talent, particularly a Junior Chair Professor, and aims to attract high-potential candidates. However, it is not entirely clear whether the new field of research has been defined yet or if the candidate's profile will dictate this area of research. Compatibility with the ongoing program will be key. The unit could also welcome developments in emerging technologies, such as spatial transcriptomics. Challenges may arise due to retirements among Inserm engineers and the high turnover of non-permanent staff, which could affect continuity in maintaining technical expertise in key research areas.

Action plan on the new challenges of research in the field
The unit acknowledges the challenges associated with using animal models in cardiovascular research, particularly in light of public concerns about animal welfare. It strictly adheres to the 3R principles and aims to use cellular models whenever feasible, including the development of organoid models with Hipsc cardiomyocytes. However, the unit maintains that many mechanisms can only be fully understood through animal models, given their integrated physiological regulation. Therefore, the unit emphasizes the importance of educating the public on the necessity of animal research for developing safe and effective medical treatments.

Planned efforts to reduce the environmental impact of the Unit activities
The unit is committed to developing ecological policies. Traveling by train for national and European conferences is strongly encouraged. Grouped orders are systematically organised to minimize environmental impact. The research and sustainable development action plan launched by UPSaclay in 2023 ensures that environmental issues, such as waste sorting, are taken into account. One main objective is to improve waste management and recycling.

Open science
The unit participates in actions to disseminate scientific knowledge to the general public. Furthermore, it encourages its members to publish their work in open-access journals, particularly under gold open-access journal licenses. The unit also deposits published articles in self-archiving sites such as HAL and BioRxiv.

Planned efforts in view of gender equality
The unit is dedicated to gender equity, ensuring that promotions are based on merit and effort while maintaining balanced representation among its permanent members. Team members have participated in Inserm training on team management and issues such as sexual and gender-based violence. Team leaders are also made aware of the risks of moral harassment, supported by dedicated referents within the unit to promote awareness and ensure a safe working environment. Overall, this seems appropriate.

Actions in favor of scientific integrity
The unit is committed to scientific integrity by adhering to the UPSaclay research ethics rules, requiring doctoral students to understand and comply with its terms and to complete training on scientific integrity before their thesis defense. New laboratory members must read and sign internal regulations that outline good research practices. To promote accountability, all data and discussions are recorded in laboratory notebooks, and weekly scientific meetings at both the unit and team levels are mandatory to ensure quality control of scientific output.

The unit has secured fundings through two international grants from Leducq foundation (until 2026) and NIH (until 2025), one European grant ANR-DFG (until 2026), and six ANR-backed projects (3 until 2025, 1 until 2026, 1 until 2027 and 1 until 2028).

Comments
The unit has set a series of defined objectives that align with current research programs. It has also worked to create favourable conditions for the development of these programs, including the advancement of new technologies. The recruitment of a new team will be key to the future organisation of the unit. Not only will it increase the scientific critical mass, but more importantly, it will provide the opportunity to introduce innovative methodologies. However, the unit has not clearly defined what these novel approaches could be. From an external perspective, it seems the unit could benefit from areas such as bioinformatics, machine learning, or spatial transcriptomics.

RECOMMENDATIONS TO THE UNIT

Recommendations regarding the Evaluation Area 1: Profile, Resources and Organisation of the Unit

1. The Unit should enhance internal communication both between teams and across all categories of personnel. Responsibility for equipment maintenance and cleaning should be clarified to ensure smooth functioning of the technical labs.
2. The Unit should clarify its positioning within basic, preclinical, and translational science. A clearer definition of its primary objectives is needed, particularly regarding its target pathology—whether the focus is pump failure, arrhythmia, or specific types of arrhythmias.
3. If translational research is a priority, it should be further developed and adequately supported. The external scientific advisory board could benefit from including more clinicians to strengthen the translational program and possibly stakeholders from the pharmaceutical industry to provide guidance on specific gene therapy initiatives.

Recommendations regarding the Evaluation Area 2: Attractiveness

1. The research programs should incorporate more high-risk, high-yield projects.
2. The unit should aim to apply for more ambitious funding opportunities, particularly ERC grants.
3. Efforts should focus on promoting younger researchers by encouraging and supporting applications for European grants, especially ERC Starting and Consolidator grants.
4. Hiring a professional bioinformatician is essential to meet the unit's needs in this critical area.

Recommendations regarding Evaluation Area 3: Scientific Production

1. The Unit should sustain its high level of scientific output.

Recommendations regarding Evaluation Area 4: Contribution of Research Activities to Society

1. The Unit should make every effort to identify patentable discoveries and actively work on valorising its intellectual property.
2. The Unit should establish a scientific advisory board that includes experts in industrial valorisation.

TEAM-BY-TEAM ASSESSMENT

Team 1: Energy signalling and cardiovascular pathophysiology

Name of the supervisor: Mathias Mericskay / Guillaume Pidoux

THEMES OF THE TEAM

Team 1 focuses on altered metabolism in cardiac disease. While new therapies entered the clinic, SGLT2i and GLP1 analogs, research is still needed into the mechanisms involved in the energy deficit of the failing heart with the aim to identify new therapeutic targets for stimulating energy metabolism and restoring mitochondrial oxidative capacities of cardiac cells. The team aims to understand the role of energy-linked signalling pathways in the myocardium, and in particular the impact of biological sex-dependent differences in these processes.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team recruited new personnel and secured funding very well, which is in line with the previous recommendations. It is less clear how well the team members efforts are integrated among the themes, and in particular, how individual expertise of team members is used in an integrated manner in the different projects.
As for the scientific recommendations, relevant follow-up studies have been performed, and initial studies on the role of non-myocyte cells of the heart, as well as inflammation, are performed. As such, logic steps have been taken in past period.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2023

Catégories de personnel	Effectifs
Professeurs et assimilés	1
Maîtres de conférences et assimilés	5
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	1
Sous-total personnels permanents en activité	**10**
Enseignants-chercheurs et chercheurs non permanents et assimilés	3
Personnels d'appui non permanents	1
Post-doctorants	2
Doctorants	2
Sous-total personnels non permanents en activité	**5**
Total personnels	**16**

EVALUATION

Overall assessment of the team

The basic research of Team 1 has been performed at an excellent level with optimal use of available resources and personnel/time for research. Main activities of Team 1 are focussed on boosting NAD, mitochondrial function, and ER stress. **Scientific production**: The publications of the team (n=48) are mostly in cardiovascular-related journals (with half of the publications with a member of the team as senior position

Recognition: The team raised 2 M€ as PI and 250 K€ as partners) but fundings appears to depend on the PI a lot (3 ANR), an international collaboration (ANR-DFG grant) and participation to a COST action Meta-Heart. Five nternational students (Canada, USA, and Germany) were hosted.

Valorisation: A collaboration with a company (G-LIFE) was established and two patents were filled but withdrawn due to the high number of competitive patents and lack of perspective for licensing.

Strengths and possibilities linked to the context

Attractiveness
Team 1 is headed by Mr. Mericskay (and Ms Garnier as co-leader), who in 2016 strengthened research on cardiac energetics in heart failure with his research line on NAD metabolism. The team uses various mouse models of HF ranging from surgery-induced HF, including myocardial infarction (MI) and transverse aortic constriction (TAC) to genetic inactivation of key players in identified signaling pathways including the energy stress sensor kinase AMPK and the metabolic regulator SIRT1 of the sirtuin deacetylases family. Main genetic mouse models focus on NAD metabolism and ER stress.
In addition, during the last mandate, there are seven PIs of whom two are retired. A member of team 2 will move to Team 1 as co-leader in January 2026. In addition, two MCUs recently joined team 1. It is a relatively large team (5 PIs, and 2 retired PIs; 4 technicians), though many have 50% teaching. The focus of the research is on NAD metabolism and ER stress, with special emphasis on sex differences. International colleagues from Lebanon and the USA visited the Team, and PhD students from Mexico and China joint the team with the support of exchange programs. Thirteen PhD students graduated in Team 1 during the last mandate. Currently, four PhD students and three post-docs are active in the team.

Recognition
Recognition is evident from 31 invited lectures (ISHR, ESC, Gordon), and awards (International Society for Heart Research - Medal of Merit, Keynote at the international meeting of the Society for Heart and Cardiovascular Metabolism). Many invitations and awards were for a retired PI member of the team. Multiple invitations to present about NAD/NR therapy were done by the leader of the team, Mr Mericskay. The topic on NAD metabolism is timely, and visible in the scientific field. Mr Mericskay leads one of the five working packages of the European Cost-Action network called EU-Metaheart.
The team raised 2 M€ as PI and 250 K€ as partners: an ERA-Net on Cardiovascular Diseases was obtained by one of the team members, and international grants were obtained by Mr Mericskay (ANR-DFG grant and COST action Meta-Heart). In addition, fellowships (750 K€) were obtained for junior people (two post-docs, three PhD students) and grants to support visiting professors from Lebanon and the USA and exchange of students from Mexico and China. Three ANR grants were obtained by Mr Mericskay as PI (428 keuro), and national foundation/charities funding for two post-docs and three PhD students.

Scientific production
The team published 48 original studies, sixteen reviews/editorials and nine book chapters in good to high impact journals of speciality (Cardiovascular Research, Circulation; top 10% of cardiovascular journals). Approximately half of the publications have a leading senior author from team 1 (23 as 1st, last or corresponding author). Overall, scientific production appears to be driven by a few PIs. The team successfully published on nicotinamide riboside kinase 2 as new regulator of NAD metabolism. Several main publications that have impact on the field have been published. A main success was the study that showed benefit from nicotinamide riboside (NR) in a model of dilated cardiomyopathy with >200 citations (published in Circulation). The team published fourteen reviews, one editorial and three book chapters. Ten publications were joint studies with PIs from Team 2 and Team 3. Two PhD students work on a project in collaboration with Team 3. Five international students (Canada, USA and Germany) worked in the team for two to five months.

Contribution of research activities to society
The team filed two patents. One related to the use of NR for the treatment of cardiomyopathies, which was withdrawn by Inserm Transfert after internal review committee evaluation due to the high number of competitive patents and lack of perspective for licensing. The second patent was related to the use of NR to blunt adverse cardiac remodelling, in particular after myocardial infarction. Also, this application was withdrawn after 2 years. A collaboration with a company (G-LIFE) was established and continued in the upcoming period. This biotech company works in the field of cardioprotection by photomodulation. Limited time has been spent on other forms of dissemination. The new place allows more contact with industrial partners.

Weaknesses and risks linked to the context

The activity of the team appears to be a rather high reliance on one/two PIs. A heavy teaching load is mentioned for some members. From the description, it is not clear which junior researchers will take the lead in future years, and if they have a heavy teaching load. While it is stated that research is done on target identification, the work involves in depth analyses of mouse models, and genetic models are used to proof relevance of a target. There is no true translation to human, though the step to using iPSC models may resolve part of this issue. The work that is done in mouse models lacks validation in patient samples/cohorts. The Pacific study cohort may be of interest for the future. Collaboration with industry/and small/medium enterprises is limited. Collaboration with clinicians is still limited, and a clear focus on disease entities is not present and very broad ranging from myocardial infarction to heart failure with preserved ejection fraction (Hfpef,) and sex differences. A clear career path for the post-docs/junior scientists in the team is currently not present.

Analysis of the team's trajectory

While new mechanisms are uncovered in mouse models, the step to clinical translation is unclear. A strategy to step to translation of data in mouse models is not present. How will the team step from studies in mouse models to human translation? Current models involve MI and TAC, which are rather traditional models. There is no clear plan of how to move newly identified targets to the clinical setting.
Rather high reliance on one/two PIs (two are retired), and relatively heavy teaching load. From the description, it is not clear which junior researchers will take the lead in future years, and if these PIs have a heavy teaching load.

RECOMMENDATIONS TO THE TEAM

The team is advised to make a clear plan to move their basic science data to translation, including active collaboration with clinical partners. In addition to the Pacific cohort, there are multiple cardiac tissue banks, including clinical data, at international colleagues which may serve to validate observations. This may also increase the success of future patent applications. In addition, looking at the future, sub-phenotyping of patients is warranted to properly link outcomes and drug response. BMI of individuals has a major impact on -omics profiles, and should receive attention.

The team is advised to more frequently use mouse models that better resemble human disease, in particular Hfpef, and benefit from human stem cell models in the institute.

External funding may be improved if PIs team up and submit joint applications, in particular (junior) individuals from the different themes. Internal pre-selection and support for individual scientists may benefit quality of the applications.

Team 2: Cyclic nucleotide signalling and cardiovascular pathophysiology

Name of the supervisor: Grégoire Vandecasteele / Jérôme Leroy

THEMES OF THE TEAM

Team 2 is specialised in the physiology and pathophysiology of cyclic nucleotides (cAMP and cGMP) in the cardiovascular system. It studies all aspects of this transduction system, from cellular compartmentalisation, regulation of cell concentrations by phosphodiesterases to pharmacological manipulations by phosphodiesterase inhibitors and therapy by viruses or peptides.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Few recommendations were given. Mainly two in fact: prepare the retirement of Mr Fischmeister and develop more translational approaches. For the first one, it will for sure not be simple but new researchers have been recruited and will take the whole lead. Concerning the second point, it is still difficult because the team is far from an hospital with a high level of clinical and fundamental research. Nevertheless, members have developed collaborations with industries and some cardiologists.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2023

Catégories de personnel	Effectifs
Professeurs et assimilés	2
Maîtres de conférences et assimilés	1
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	1
Sous-total personnels permanents en activité	**7**
Enseignants-chercheurs et chercheurs non permanents et assimilés	42
Personnels d'appui non permanents	1
Post-doctorants	2
Doctorants	5
Sous-total personnels non permanents en activité	**10**
Total personnels	**17**

Overall assessment of the team

Team 2 was evaluated excellent.
Scientific production: This team has published 59 publications in the higher-level journals of the field (Circulation (3 papers, 2 as principal investigators), Cardiovasc Res (2 as principal investigators), J Am Heart Assoc, Circ Res, J Mol Cell Cardiol …). The team gave new insight on the compartmentation of cyclic nucleotide signalling (nuclear and mitochondrial cAMP/PKA pathway, cardiac β-ARs in T tubule…), on the regulation of cardiac and vascular function by the cAMP (relaxing effect of PD3 and PDE4 inhibitors).

Attractivity: The team has demonstrated success in international (Leducq, ERA-CVD as PI) and national calls (9 ANR with 6 as PI) as for a total amount of 3.8 M€. They were invited to give 36 conferences in congresses (Gordon, ISHR, ESC…). Fifteen PhD students graduated during the last mandate, and four are ongoing.

Valorisation: The team has developed several industrial partnerships (Pfizer, Sanofi) with one Cifre contract obtained with Sanofi.

Strengths and possibilities linked to the context

Attractiveness
The team was restructured at the beginning of this mandate and now has eleven permanent researchers, four of whom are part-time. Technical support is provided by the equivalent of two IEs/technicians and 33% secretarial staff. Permanent researchers are divided between four researchers (DR or CR) and three teacher-researchers. The laboratory welcomes Masters (2 currently), PhDs and post-doctoral fellows (5) from France and different countries (Liban, Brazil, China…). Fifteen PhD students graduated in Team 2 during the last mandate.
This team proposes a translational approach aimed at developing new therapeutics, through three axes.
Team 2 is part of the doctoral school 569 "Therapeutic innovation", with Mr G Vandecasteele directing the "Molecular and Cellular Pathophysiology" division.

Recognition
The team is identified as a leader in the field. The researchers involved are regularly invited to give conferences (n=36) in national (GRRC, French Society of Cardiology) and international congresses (Gordon, ISHR-ES, European Society of Cardiology). It participated to the organisation of the IHR-ES in 2018, 2023 and 2024 and to the Printemps de la Cardiologie from 2013-2024 (n=14).
Team received four international prizes from International Society for Heart Research and International Academy of Cardiovascular Sciences.
The team has recurrent resources (salaries and staffing) and has demonstrated success in international and national calls during the last mandate. Members of the team are investigators in national grants from PIA (coordinator of Labex Lermit), from ANR (4/5 ANR contracts as PI, PKAIHEART, CardioTarget, Cardiopeg and PDEtreat4Heart), 1 as co-PI (Signalage); one Inserm Installation package (PI). The team obtained international grants (Leducq (co-PI); Program Hubert Curien Cedre (Liban) and Xu Guangqi (PI)) grants. Thus, more than 3.8 €million was obtained directly for the laboratory in calls for several laboratories or just one. Young PI obtained a grant from "Federation Française de Cardiologie".

Scientific production
The scientific production is high (59 publications, (20 as 1st, last or corresponding author), twenty reviews/editorials and two book chapters, regarding the number of researchers. They publish in the higher-level journals of the field (3xCirculation, 2 as PI), 2xCardiovasc Res (as PI), J Am Heart Assoc, Circ Res, J Mol Cell Cardiol …) and sometimes in general journal as collaborators (Nature Rev Cardiol, Life Sci, Nat Commun. We can also underline numerous papers in journals of pharmacology (Pharmacol Ther (1), Br J Pharmacol (2), Eur J Pharmacol (1) all as principal investigators. Team members are also participated in editorial committee (Circulation, Cardiovasc Res, Vascular Physiol,..).

Contribution of research activities to society
The team has developed several industrial partnerships (Pfizer, Sanofi) with one Cifre contract obtained with Sanofi. The laboratory develops targeting tools to the myocardium i.e., peptide ligands (collaboration with Sanofi). Due to their basic research activity the team does not target communication to the general public.

Weaknesses and risks linked to the context

This team proposes a translational approach aimed at developing new therapeutics, even if the fundamental aspects seem to be more at the heart of their concerns, the valorisation of the fundamental research needs be developed. Developing drugs is an issue by itself with many constraints (economic, placement of the compound regarding other therapeutics, size of the market, industrial competition in the field, complexity of the compound).
The in vivo experimental approaches are limited to small animals (mice) that are not fully representative of the human situations. The absence of works in larger species appears as a limitation.

Analysis of the team's trajectory

Pushed by the former director of the unit (Mr Fischmeister) expertise and scientific international recognition, the team developed and is now located in an area able to help for recruitment and technical support. The new location of the laboratory offers an environment ideal for the access to technical platforms and to establish connections with other local laboratories. The centre is classified as a centre of excellence aiming at pushing biomedical research.

RECOMMENDATIONS TO THE TEAM

Even if working in basic cardiovascular science, the team emphasizes that it works to find new treatments. It seems that the team should establish collaborations with cardiologists and research centres specialised in cardiac arrhythmias. They could help to better define the positioning of their therapeutic approaches within the current therapeutic panel. An in-depth discussion has to be conducted to define the position of PDEA4 activators in face of beta blockers but also defibrillators and/or antiarrhythmics.

Team 3: Calcium signalling and cardiovascular pathophysiology

Name of the supervisor: Ana María Gómez / Jessica Sabourin

THEMES OF THE TEAM

The team focuses on: 1) Alterations in calcium influx through L-type calcium channels and store-operated calcium channels in heart failure; 2) Role of ryanodine receptor (RyR2) in normal rhythm and arrhythmias, including genetic diseases like CPVT (Catecholaminergic polymorphic ventricular tachycardia); 3) Role of Epac (exchange protein activated by cAMP) signalling in cardiac pathology, especially in diabetic cardiomyopathy and chemotherapy-induced cardiotoxicity. The team employs an integrated approach from molecules to whole animals, using transgenic models, pathological animal models, and human iPSC-derived cardiomyocytes to understand calcium dysregulation mechanisms and identify new therapeutic targets.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous evaluation made three main recommendations:
1-On scientific production: Explore potential patenting of findings.
The team indicated their findings were of basic nature and did not allow patent filing.

2-On team organisation: Consider sharing leadership tasks with next generation following new recruitments. The team recruited two new members (one associate professor in 2020 and one hospital-associate professor in 2023). The current Team director, Mr. JP. Benitah, will step down at the end of the current contract, promoting Ms J. Sabourin as team co-director.

3-On scientific strategy: Add riskier projects to open new directions

The team has extended their research by Implementing new tools like Hipsc-CMs and large animal models (rabbit KI and pigs), by adopting new techniques including super-resolution microscopy and optical mapping, by exploring transcriptomics, by investigating new fields like circadian regulation of ionic currents and by proposing a new risky project towards personalised medicine in CPVT

WORKFORCE OF THE TEAM: in physical persons at 31/12/2023

Catégories de personnel	Effectifs
Professeurs et assimilés	2
Maîtres de conférences et assimilés	4
Directeurs de recherche et assimilés	2
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	1
Sous-total personnels permanents en activité	**9**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	0
Post-doctorants	0
Doctorants	6
Sous-total personnels non permanents en activité	**6**
Total personnels	**15**

EVALUATION

Overall assessment of the team

Team 3 demonstrates an excellent scientific productivity and international recognition in cardiovascular pathophysiology research. Their integrated approach from molecular to clinical studies, strong publication record in top journals, and successful funding track record are notable strengths.

Attractiveness: Team 3 demonstrates robust attractiveness in cardiovascular pathophysiology research by 1/securing funding for a total amount of 2 M€ (NIH 2020 (R01), Europe Rise H2020, 2ANR (Nacar, Ifor) as PI and 1 Leducq Foundation as partner).2/ the team has recruited one MCU and one MCU-PH during the last mandate and 3/ eleven PhD theses were completed during the mandate and seven PhD are ongoing.

Scientific production: The team has publishing 60 original articles (23 PDC) in high visibility journals of cardiology (including Circulation and Circulation Research). They have identified the role of RyR2 in normal rhythm and arrhythmias and the role of Epac/Ca2+ in the context of diabetes and of cardiooncology
Team 3 actively contributes to society through the organisation of international courses (Rise, EHRA) and participate in Healthi and Eugloh initiatives, promoting transdisciplinary research.

Contribution to society: Team 3 actively contributes to society through the organisation of international courses (Rise, EHRA) and participate in Healthi and Eugloh initiatives, promoting transdisciplinary research.

Strengths and possibilities linked to the context

Attractiveness
Team 3 demonstrates robust attractiveness in cardiovascular pathophysiology research by securing funding for a total amount of 2 M€ (e.g., NIH as PI, Rise H2020 as co-PI, 2 ANR obtained during the mandate as PI and 1 Leducq as partner) and attracting talent (11 PhD theses completed since 2018). The team has state-of-the-art equipment, global collaborative network, and expertise in cardiac electrophysiology and Ca2+ imaging contribute significantly to their appeal.

Recognition
The team leaders (but less the junior PIs) have a significant recognition in their field, evidenced by editorial roles in high-impact journals (JMCC, Europace) and leadership positions in prestigious scientific societies (ESC, ISHR), and the President's Distinguished Lecture award. The organisation of 23 scientific meetings and numerous international invitations (36 meetings, 24 seminars) further attest to their standing.

Scientific production
Team 3's scientific output is impressive, with 60 original articles (23 as first, last, or corresponding authors) in high visibility journals of cardiology (including Circulation and Circulation Research), 25 reviews/editorials (17 first, 18 last, 18 corresponding authors), and eight book chapters. Their collaborative activity is evident in 57 joint publications, with 30 being international. The dissemination of research through 142 conference abstracts demonstrates active engagement with the scientific community. All permanent staff contributes to this productivity, with each student leading at least one publication. The team adhere to open access policies and scientific integrity principles, including the use of Inserm laboratory books.

Contribution of research activities to society
Team 3 actively contributes to society through the organisation of international courses (Rise, EHRA) and participate in Healthi and Eugloh initiatives, promoting transdisciplinary research. The team engages in public outreach via workshops, school visits, and events like "Fête de la Science". They disseminate research through social media, open access publications, and media appearances. Collaboration with clinicians enhances translational impact. Team members contribute to the scientific community through editorial roles and grant evaluations.
While they host students at various levels and participate in university outreach, there's potential to enhance engagement with patient associations and develop more structured public programs. Expanding industry collaborations and interdisciplinary research could further enhance their societal impact.

Weaknesses and risks linked to the context

Research Focus and Interdisciplinary Expansion
The team's strong focus on cardiovascular pathophysiology, while a strength, also presents potential limitations. There's a risk of missing out on breakthroughs that could come from interdisciplinary research. Exploring connections between cardiovascular health and other systems like the nervous or immune systems could open new research avenues. This narrow focus might restrict opportunities for cross-disciplinary collaborations and limit the team's ability to address broader health challenges. The risk of becoming too specialised could potentially reduce the team's adaptability to emerging research trends or funding opportunities.

Clinical and Industry Connections
Limited local clinical connections hinder MD student recruitment and potentially restrict the translational impact of their research. This weakness could lead to a gap between basic research and clinical applications, potentially reducing the immediate relevance of their findings to patient care. The team's industry collaborations have room for growth. Insufficient industry partnerships risk limiting access to resources, novel technologies, and pathways for translating research into commercial applications. There's also a risk of falling behind in the competitive landscape of translational research if these connections are not strengthened.

Infrastructure and Resource Management
Dependence on specific funding sources (e.g., ANR, NIH 2020 (R01), Europe) poses a risk to research continuity if these sources become less available. Variability in productivity among team members could lead to inefficient resource allocation and potentially impact the team's overall output. There's a risk of losing competitive edge if infrastructure gaps are not addressed promptly.

Societal Engagement and Local Visibility
The team's visibility and prominence within the immediate research community and nearby clinical centres appear to be areas that could be strengthened. Limited local visibility could result in missed opportunities for collaborations, talent acquisition, and resource sharing within the immediate research community. Insufficient engagement with patient associations risks developing research directions that may not align with patient needs or priorities. The lack of structured public outreach programs could lead to reduced public understanding and support for their research. There's a risk of diminished societal impact and potential difficulty in demonstrating the broader relevance of their work to funding bodies and policymakers if these aspects are not improved.

Analysis of the team's trajectory

Team 3's research plan focuses on several (too many?) key objectives in cardiovascular research, primarily centred on calcium signalling and its role in cardiac function and dysfunction: 1) RyR2 phosphorylation in stress-induced chronotropic effects (role of PKA-dependent phosphorylation site S2030 on RyR2 during cardiac adrenergic response, using novel knock-in mouse lines); 2) Define the mechanisms of circadian rhythm in cardiac Cav1.2 expression, potentially dependent on RORa, a key component of the biological clock; 3) Mechanisms of genetic arrhythmogenic diseases: The team will focus on CPVT and Ogden disease, using both knock-in mice and rabbit models, as well as Hipsc-CMs from patients; 4) Dyad modulation in heart failure: They plan to investigate the remodeling of dyads in experimental HF models and human myocardial samples, focusing on both Hfref and Hfpef; 5) Orai1 and STIM1/2 modulators in HF: The team aims to confirm the translational relevance of Orai1 inhibition in preclinical models of left and right HF, with a focus on sex differences and 6) Epac's role in cardiac dysfunction and remodelling: They will study Epac's contribution to Hfpef development and its role in cardiotoxicity following anticancer therapy.

The focus on circadian regulation of Cav1.2 and the investigation of Orai1 as a potential therapeutic target in HF represent innovative directions. The team's work on CPVT has already yielded novel insights, such as the discovery of nanostructural alterations in RyR2R420Q mutation. The research strategy employs a multidisciplinary approach combining molecular, cellular, and in vivo studies using state-of-the-art techniques such as super-resolution microscopy, optical mapping, and transcriptomics.

The potential clinical impact is significant: their work on RyR2 phosphorylation could lead to new treatments for arrhythmias. The Orai1 inhibition studies could potentially repurpose Auxora™ for clinical trials in HF treatment. The focus on sex differences in Hfpef could contribute to more personalised treatment approaches. Their research on Epac in cardio-oncology could improve outcomes for cancer patients by mitigating treatment-induced cardiotoxicity. They have fundings from various sources, including NIH and ANR grants until 2028.
However, the team's trajectory shows limited progress in some areas highlighted by previous evaluations:

Patenting and Industry Interactions: Despite previous recommendations, there's no evidence of new patents filed. Industry interactions remain limited to two contracts with Sanofi and Cydan.

Research Direction: While the team has expanded into new areas like cardiotoxicity of anticancer drugs, their strategy largely continues along established lines. The recommendation to add riskier projects has not been fully addressed.

Clinical Translation: The team's interaction with clinics remains weak, with no clear bench-to-bedside translation efforts reported.

RECOMMENDATIONS TO THE TEAM

Translational Research:
The team should 1) strengthen clinical collaborations for translating findings into applications; 2) focus particularly on promising areas like Orai1 inhibition for heart failure; 3) increase use of human samples and patient-derived cells and 4) better define clinically relevant endpoints
Areas for improvement include strengthening local hospital connections which are limited to facilitate MD student recruitment. Enhancing industry partnerships (a previous HCERES comment) and local visibility could further elevate their attractiveness and expand their influence in cardiovascular research.

Industry Relations and IP:
The team should more actively pursue patent opportunities, especially for RyR2 modulation and Orai1 inhibition, develop stronger industry partnerships and consider creating spin-offs where appropriate.

Interdisciplinary Growth:
The team should 1) expand collaborations with experts in genetics, bioinformatics, systems biology; 2) integrate new methodologies from other fields and 3) participate in interdisciplinary research programs.

Leadership Development:
The team should 1) create formal mentoring program for emerging leaders; 2) delegate project leadership to younger researchers; 3) establish sub-team structure with rotating leadership and 4) provide leadership training opportunities.

Clinical Integration:
The team should 1) build stronger ties with medical centers; 2) increase recruitment of clinician-scientists; 3) focus on addressing unmet clinical needs and 4) develop more clinical research protocols.

Innovation and Risk-Taking:
The team should 1) consider adding higher-risk/higher-reward research directions and 2) explore new signalling pathways beyond established tracks.

CONDUCT OF THE INTERVIEWS

Date

Start: 22 novembre 2024 à 08h00

End: 22 novembre 2024 à 08h00

Interview conducted: online

INTERVIEW SCHEDULE

Cardiovascular signalling and pathophysiology (CARPAT)
November 22, 2024
Hceres committee: M Thierry PEDRAZZINI (president), Ms Giuseppina CALIGIURI (CSS3, Vice-president), M Laurent MONASSIER, Ms Jolanda VAN DER VELDEN, M Benjamin GRENIER-BIOLEY (PAR)
Conseiller scientifique Hceres : Mme Florence PINET

08h30 Presentation of the committee

08h45-09h25Highlights of the Unit by the Directors (20min presentation+ 20min questions)

09h25-09h50Team 1: Energy signalling and cardiovascular pathophysiology: **M Mathias Mericskay / M Guillaume Pidoux** (15 min présentation : 10 min questions)

09h50-10h15 Team 2: Cyclic nucleotide signalling and cardiovascular pathophysiology**: M Grégoire Vandecasteele / M Jérôme Leroy** (15 min présentation : 10min questions)

10h15-10h40 Team 3: Calcium signalling and cardiovascular pathophysiology**: Ms Ana María Gómez / Ms Jessica Sabourin** (15 min présentation : 10 min questions)

Coffee break: 10 mn

10h50-11h45 Committee debriefing

11h45- 12h15 Meeting with the representatives of the local institutions **(closed doors)**
Inserm IT : Raymond Bazin
Inserm Delegate: Philippe Arhets
Université Paris Saclay VP Recherche déléguée Santé et Sciences de la Vie : Anne Monsoro-Burq et VD Recherche faculty of pharmacy: Elias Fattal

12h15-13H00 LUNCH

13h00-13h30 Meeting with technicians and administrative staff (closed doors) in French

13h30-14h00 Meeting with PhD and post-doc (closed doors)

14h00-14h30 Meeting with researchers not team leaders **(closed doors)**

Coffee break: 15mn

14h45-15h15 Closed doors meeting of the committee

15h15-15h45 Meeting with the Directors (present and future)

15h45-17h30 Committee meeting (closed doors)

PARTICULAR POINT TO BE MENTIONED

N/A

GENERAL OBSERVATIONS OF THE SUPERVISORS

The institution responsible for submitting the application, which is also responsible for coordinating the response on behalf of all the research unit's supervisors, did not submit any general observations.

The Hcéres' evaluation reports are available online:
www.hceres.fr

Evaluation of Universities and Schools
Evaluation of research units
Evaluation of the academic formations
Evaluation of the national research organisms
Evaluation and International accreditation

Evaluation · Research · Higher Education
Hcéres

19 rue Poissonnière
75002 Paris, France
+33 1 89 97 44 00