BC2M - Biocommunication en cardio métabolique

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on research units and interdisciplinary research units

BioCommunication en Cardio-Métabolique

BC2M

Under the supervision of the following institutions and research bodies:

Nouvelle Université de Montpellier

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

January 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. Pierre GOURDY, 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 independent and collegial deliberation of the committee.

Unit name:	BioCommunication en Cardio-Métabolique
Unit acronym:	BC2M
Label requested:	UMR_S
Present no.:	EA 7288
Name of Director (2013-2014):	Ms Anne-Dominique LAJOIX
Name of Project Leader (2015-2019):	Ms Anne-Dominique LAJOIX

Expert committee members

Chair:	Mr Pierre GOURDY, Université de Toulouse
Experts:	Ms Marie-Christine ALESSI, Université Aix-Marseille
	Mr Emmanuel DROUET, Université de Grenoble (representative of the CNU)
	Mr Christophe MAGNAN, Université Paris Diderot
	Mr Ronan ROUSSEL, Université Paris Diderot
	Mr Pierre-Louis THARAUX, Université Paris Descartes
	Ms Cécile VINDIS, Université Toulouse (representative of CSS INSERM)

Scientific delegate representing the AERES:

Mr Jean GIRARD

Representatives of the unit's supervising institutions and bodies:

Mr Christian JORGENSEN (representative of Doctoral School CBS2 n°168)

Mrs Chantal LASSERRE, INSERM

Mr Jacques MERCIER, Université de Montpellier

1 • Introduction

History and geographical location of the unit

The CIPD (Center for Pharmacology and Innovation in Diabetes, CNRS UMR 5232, Pr P. PETIT) has been created in January 2007, as an evolution of the previous CNRS UMR5160. Renewal of the unit occurred in 2011 with the integration of another local research team (EA3127) developing clinical and experimental research projects in the field of kidney and hypertension. The CNRS FRE3400 (Pr A. LAJOIX) has been created in January 2011, but CNRS national committee requested a mid-term evaluation.

This CNRS mid-term evaluation has been conducted in 2012 (spring) and did not support the creation of a CNRS UMR. The loss of the CNRS label led the Montpellier 1 University to propose the creation of the EA7288 (Pr A. LAJOIX) in January 2013.

The unit is located at the UFR of Pharmacy, 15 avenue Charles Flahaut, BP 14491, 34093 Montpellier.

Management team

Since 2011, the unit leader is Ms Anne-Dominique LAJOIX who is University Professor at the UFR of Pharmacy, Nouvelle Université de Montpellier (NUM). The unit includes two distinct thematic groups (work packages) respectively headed by a CR1 INSERM and a DR2 CNRS.

AERES nomenclature

SVE1_LS4, SVE1_LS3

Unit workforce

The global manpower of the unit is thought to remain quite stable in the new project, but it is of note that one permanent researcher involved in scientific theme 1 will retire within a few weeks (March 2014). Current and future unit workforces are detailed in the following tables.

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
N1: Permanent professors and similar positions	5	6
N2: Permanent researchers from Institutions and similar positions	3	2
N3: Other permanent staff (without research duties)	4	4
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)		
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	3	3
N6: Other contractual staff (without research duties)	1	1
TOTAL N1 to N6	**16**	**16**

Unit workforce	Number as at 30/06/2013	Number as at 01/01/2015
Doctoral students	2	4
Theses defended	10	
Postdoctoral students having spent at least 12 months in the unit*	6	
Number of Research Supervisor Qualifications (HDR) taken	4	
Qualified research supervisors (with an HDR) or similar positions	11	10

2 • Overall assessment of the interdisciplinary unit

The current unit has been created in 2011 but lost its CNRS label in 2012 after a mid-term evaluation, leading to the creation of the EA 7288 (Pr A. LAJOIX) in January 2013. The unit includes 2 work packages which developed quite heterogeneous projects in the respective field of 1) hypertension and kidney/vascular damages; 2) insulin secretion and dysmetabolism. Their association is quite recent and only a few interactions have been established until now, but good experimental works have been published recently. The present project aims to explore how the metabolic syndrome, especially the secretome of adipose tissues, influences insulin secretion and impacts the kidney and the vascular system. New partnerships have been established with clinicians to collect human plasma/tissue samples during bariatric surgery and to develop translational studies mainly based on omic approaches. Overall, scientific questions are relevant but the committee considered that the global project is somewhat over-sized according to the unit size. Furthermore, clear mechanistic hypothesis-driven strategies are lacking to optimize the final ambition of the project. However, the committee acknowledges the dynamism of the team leader, the strong implication of all team members, the good involvement in teaching and training through research, and the very well recognized interaction with the local economic environment. Finally, the committee underlines the need to improve the scientific interactions between researchers, students and clinicians and to recruit permanent researchers in the next years.

Strengths and opportunities related to the context

- Dynamic team leader and consensus of the team members;

- Relevant up-to-date societal questions about co-morbid conditions linking the metabolic syndrome with alterations in insulin secretion and with kidney/vascular damages;

- Good level of recent original publications;

- Building of strong clinical partnerships to develop biobanks and translational research;

- Very good interaction with the economic environment and capacity to raise private money;

- Good involvement in training through research;

- Coherence with the governance of Montpellier University.

Weaknesses and threats related to the context

- Difficulty for the team to improve its international reputation/visibility in such a competitive field of research;

- Lack of hypothesis-driven programs which could improve the global ambition of the project;

- Low level of publications in direct relationship with the project and low citation indexes;

- Oversized project according to the current workforce of the unit;

- Aging of researchers with the most significant expertise in specific experimental domains;

- Scientific management is not optimal to favor interactions, especially between researchers and clinicians but also with students and other members of the team;

- Few competitive large public grants.

Recommendations

- Better identification of mechanistic hypotheses that will drive the experimental strategy for both animal and translational studies;

- Considering additional tools/animal models to explore the relationship between adipose tissue secretome, inflammation and specific end-points to improve the mechanistic ambition of the project;

- Favoring interactions between the 2 workpackages, and especially with the clinicians involved in the project;

- Lab meeting should be more formal to improve interactions between researchers and with students;

- Clinicians involved in the project should systematically participate to these lab meetings;

- Recruitment of permanent researchers to reinforce both thematic groups, then to maintain the expertise in specific domains when members of the present staff will retire.

3 • Detailed assessments

Assessment of scientific quality and outputs

The team leader is assisted by a senior researcher for work package 1 (Modulation of cardiac/renal risks in hypertension and metabolic dysfunctions). This small size group has a long track of publications mainly related to the effect of sodium restriction on vascular health, and interaction of large arteries dysfunction with microvascular function at target-organ level. An important part of the papers included in the report are purely clinical and the contribution of the whole research group to their production is not always clear. Furthermore, the real interaction between experimental researchers and clinicians seems to be quite limited. The recent axis of research is the reciprocal effects of metabolic abnormalities, and especially perivascular fat deposition, with arteries function in the context of sodium intake. This topic is in line with study by group 2 of the influence of peripancreatic fat on inflammation and pancreas function. Very few papers have been produced by the team on this recent topic, which is transversal in the group. Of note, a few abstracts involving both groups of the team have been presented at meetings. Their number is expected to increase in the mid-term.

The team leader is assisted by a senior researcher for work package 2 (Beta cell alterations in prediabetes and obesity). The main objective will be to identify new mechanism of regulation and to develop new protective strategies against metabolic stress and inflammation. This project is also based on a small size group working together since 2007. The group already evidenced original mechanisms as potential regulators of B cell function: 1) Expression of purinergic receptor P2Y subtypes in pancreatic B cells of rats and in humans islets, whereas the functional role of these subtypes remains unclear; 2) Contribution of nNOS and IL1β in both insulin secretion and insulin resistance. In B cells a role for PIN (protein inhibitor of nNOS) was evidenced as a modulator of nNOS activity and consequently insulin secretion. Another important theme of the group is “drug discovery”, especially anti-diabetic compound. Three main approaches have been studied: inhibitors of nNOS-PIN complex, inhibitors of iNOS, and inhibitor of glycogen phosphorylase. Research projects have been supported by several local or national fundings, but no grant from the European Union. These topics already led to patents and new patent registrations are planned in relation with the recent identification of nNOS-PIN complex inhibitors. The group has also access to a collection of “plant extracts” and identified two compounds which could increase insulin secretion.

It is also of note that many original publications provided in the scientific production of the group (at least 26 out of 114) do not focus on the proposed priority themes. The majority of them is focused on clinical works out of the scope of the unit (immunity, bone mass acquisition and thyroid disorders). In addition, only four articles actually reflect a collaborative effort between members of the group (ie the contribution of NO in insulin secretion, inflammation and diabetes and the antihyperglycemic effect of nutrients). Regarding the “drug discovery” theme, several publications (Fund Clin Pharmacol, 2013; J Ethnopharmacol 2013) as well as patents are mentioned.

Finally, the number of citations (at the global or individual levels) is very limited, probably reflecting limitations in pioneering works. However, the committee underlines that the publications recently produced by the experimental team, alone or in interaction with the clinicians, are of a good level.

Assessment of the unit's academic reputation and appeal

The team developed a few collaborations at the local, national and international levels, but it is of note that co-authored papers are very limited. Academic collaborations have been mainly developed on the basis of the expertise of the group in nNOS function and insulin secretion. Significant invitations to international meetings are also very sparse and the international visibility of team members is thus limited. There is no foreign student or post-doctoral fellow probably reflecting a lack of recognition and attractiveness.

Both groups obtained significant grants and fellowships in the fields of hypertension and diabetes, mainly from local or national societies. The team leader obtained in 2008 a regional FRM award highlighting the originality *of the obtained results (nNOS and insulin secretion). A large partnership (COMET project) is currently under development with the Servier laboratories and the Société d’Accélération et de Transfert Technologique en Languedoc-Roussillon (SATT AxLR).*

Patents have been filled in the field of angiogenesis by members of topic 1 (out of the scope of the present project) and on molecules able to stimulate insulin secretion in 2006/2007 by members of topic 2. Several members of the unit are reviewers for international journals.

The unit leader is in charge of the organization of an annual national scientific symposium sponsored by Sanofi.

The committee finally underscores that good senior scientists are retiring or will retire after the next 5 year period with no clear perspective of recruitment of young scientist on similar INSERM or CNRS tenure position.

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

The scientific questions addressed by the unit are relevant in the context of the westernized societies: impact of sodium intake on vascular health and modulation of this impact by metabolic abnormalities, relationship between obesity, inflammation and dysfunctions of endocrine pancreas.

The team has a good implication in research development. Interesting collaborations with three small start-up companies involve both groups of the unit with patents (but no license so far) and overheads. More specifically, 2 patents on natural biomolecules and patent applications of nNOS-PIN inhibitors screened from the bank of Elderis company have been recorded. A start-up named “Gingko Sfere” has been created in 2009 by ex-members from the unit to promote their bioresource of Mediterranean plants. The CNRS magazine wrote an article about the company that was included in its international edition. As previously mentioned, the team leader received a regional price from FRM in 2008 for its work in “nNOS-PIN complex as a regulator of insulin secretion”, and this event was reported by two newspapers (“Le Midi libre”, “Journal de l’innovation”).

A partnership is currently developed with the SERVIER laboratories, the CHRU Montpellier, the SATT AxLR and the Languedoc Roussillon region (COMET project). This ambitious translational reserch project will be funded by SERVIER, SATT and FEDER financial support.

As mentioned above, members of the team actively participate in the organization of a national annual meeting “Les journées de l’innovation en diabétologie de Montpellier” with the Sanofi Diabetes Division.

Assessment of the unit's organisation and life

The organization of the team is consistent with the project aiming to study interactions between metabolic dysfunctions and cardio/renal complications. The committee acknowledges the dynamism of the team leader and the strong consensus of team members to support the proposed project. However, the experimental and clinical components of the team appear to be too separated, losing the opportunity of generating new hypotheses to be tested. Among the experimental researchers themselves, the interactions have to be more formalized. The lack of recurrent formal lab meetings with thorough discussions of data and strategy probably also impacts the awareness of students and technicians of ongoing projects. Lab meeting are planned every 2 weeks but have to be more structured to improve interactions between researchers and with students. Clinicians involved in the project should systematically participate to these lab meetings.

As the team leader is much more involved in the topic 2, due to her research background, decisions related to research policy of the entire team as a group have to be discussed collectively, and this point is not clearly stated in the project.

Assessment of the unit's involvement in training through research

The group members supervised several master students and Ph.D students during the last 5 years (10 theses defended until the end of June 2013, as recorded in the table, and 1 in December 2013) until December 2013). Students themselves and the head of the local doctoral school (Sciences chimiques et biologiques pour la santé, CBS2) acknowledged that students happily choose this small/medium size lab. The delegate of the doctoral school also confirmed that the team is fully engaged in teaching in undergraduate and graduate programs. The team members actively participate in teaching tasks, especially in pharmacoloy, immunology, biotechnologies. The team leader is part of the steering committee of the master course and is responsible for the master course “therapeutic innovation” involving several members of the group. The team also contributed to the creation of a new master 1 and 2 “BIOTIN” since 2011.

Assessment of the strategy and the five-year plan

The project is consistent with the previous works and expertises of the members of the team. Both group 1 and group 2 share relevant up-to-date questions about co-morbid conditions linking the metabolic syndrome with kidney failure or damage, hypertension and end-organ damage. However, the proposed project will bring the team in a very competitive area.

Interestingly the team proposes to further integrate human aspects in the basic research developed by both subgroups. This translational aspect between experimental research and clinic is somewhat an important point of the project. For instance, the COMET project, already funded (Servier laboratories, SATT and FEDER) will provide a large biobank of fluids and metabolic tissues from obese patients who require bariatric sugery (600 patients expected in 3 years). These patients will be classified according to insulin resistance status and familial history of diabetes. Another project (BASTOD) is supported by a local grant (Clinical research funding from the CHU Montpellier) to explore the effect of bariatric surgery on vascular and cardiac functions. Inclusions are ongoing with the aim of 90 patients enrolled.

Strikingly, the committee underlines a lack of hypothesis-driven programs which could give an optimal structure to the project. For example, regarding topic 1, after pioneering work deciphering a pro-inflammatory role of high sodium chloride diet, no hypothesis is made about the mechanism and proposed clinical approaches will only allow correlation studies. A similar comment applies to theme 2 since the part related to the interaction between secretome of fat depots and pancreatic insulin secretion is insufficiently precise which hampers the assessment of the chances of success. The questions of the influence of peripancreatic fat on insulin secretion is highly relevant but should be more precisely addressed. Regarding animal studies, Zucker fa/fa rats are certainly limited models to target B cell function, and no information has been provided about strategy and models would be used to get new insights into the mechanisms involved (such as cre-lox mice models for instance…).

Most parts of the project are based on the use of human samples from obese patients and rely on “unbiased” approaches such as proteomics/secretome studies. However, the data of the original approach on secretome will not be available rapidly, as they will be produced by external entities (responsible for omics and bioinformatics in the COMET project), and the translation to experimental work is thus hypothetical in the next years. Furthermore, efforts are probably needed to connect the clinical studies with the original experimental activity of the team, for example on immunomodulation of the vascular function or vascular calcifications.

Finally, the major challenge during the future years will be to manage the team expansion. Indeed, the proposed project seems somewhat to be over-sized according to the current team workforce. It will be very important to recruit permanent researchers to reinforce both thematic groups, then to maintain the expertise in specific domains when members of the present staff will retire. It will be also crucial to improve interactions between the 2 thematic groups, and especially with the clinicians involved in the project.

4 • Conduct of the visit

Visit date:	Wednesday 29th January 2014
Start:	10.00 am
End:	5.00 pm

Visit site :	Faculté de Pharmacie
Institution:	Université Montpellier 1
Address:	15, avenue Charles Flahaut, BP 1491, 34093 Montpellier

Conduct or programme of visit:

10.00-11.00 am	**Welcome and meeting behind the doors:**
10.00-10.30 am	Expert committee members with AERES scientific delegate (DS)
10.30-10.45 am	Expert committee members with DS and team leader
10.45-12.50 pm	**Public presentation and discussion:**
	- Team leader intervention: past and future projects 10.45-11.30 am
	- Discussion with team leader and other team members 11.30-12.30 pm
	- Synthesis by the expert committee members 12.30-12.50 pm
12.50-2.00 pm	**Lunch**
2.00-2.30 pm	**Specific discussions with:**
	- Researchers (scientists and clinicians)
	- PhD students and post-doctorants
	- Engineers and technicians
2.30-4.30 pm	**Synthesis meeting behind the doors**
	- Discussions with delegates from local institutions
	- Expert committee members with DS

5 • Supervising bodies general comments

Université Montpellier 1

AES Droit, Sc. politique Économie IPAG ISEM Médecine Odontologie Pharmacie STAPS

nouvelle université de Montpellier
un projet, une ambition

Monsieur Didier HOUSSIN
Président de l'AERES
Monsieur Pierre GLAUDES
Directeur de la section des unités de recherche
Agence d'Evaluation de la Recherche et de l'Enseignement Supérieur (AERES)
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Montpellier, le 24 avril 2014

Référence : AD. LAJOIX : S2PUR150008637 BC2M Bio Communication Cardio Métabolique. 0342321N

Messieurs,

Je tiens à remercier le comité de visite AERES pour la qualité de son rapport d'évaluation concernant l'équipe de recherche « Bio Communication Cardio Métabolique » dirigée par le professeur Anne Dominique LAJOIX.

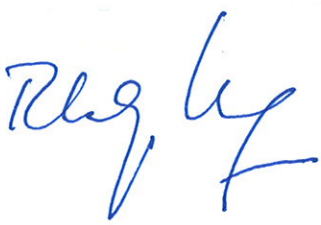
J'ai bien noté les remarques formulées par le comité de visite et je veillerai à ce que celles-ci soient prises en compte par la directrice de cette structure de recherche.

Vous trouverez ci-joint les corrections factuelles et les observations générales formulées par la directrice.

En tant que tutelle Universitaire de cette structure de recherche, je n'ai pas de remarques supplémentaires.

Je vous prie d'agréer, Messieurs, l'expression de mes salutations les plus respectueuses.

Philippe AUGE
Président
Université Montpellier 1



Montpellier le 15 avril 2014

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Response to the AERES report

Biocommunication en Cardio-Métabolique (BC2M)

E2015-EV-0342321N-S2PUR150008637-006600-RT

1) “Low level of publications in direct relationship with the project and low citation indexes”

As mentioned by the evaluation committee (page 6), the association between the two work packages was initiated in January 2013. Before 2013, they were two independent teams of the research unit, explaining the few transversal productions of the group. However, as mentioned page 8, this number will increase in the future.

In January 2013, our two programs converged in a new project, with a great originality as compared to what is done locally and nationally. This association led us to reduce some research programs (mainly for work package 2), explaining why some publications are not related to the present project. Moreover, it should be noticed that several scientists have changed their research topics when they joined the laboratory (S. Péraldi-Roux and F. Castex). However, I do believe that productions of work package 1 are clearly in line with the new project. The committee should have made this distinction.

The low citation index could be interpreted in many ways. For me, it reflects the great originality of our research topic, as very few, even none other groups is working on the same subjects (nNOS-PIN, sodium restriction). This originality does not keep us from being published in high impact journals that are red by the scientific community of our research field.

2) “Lack of hypothesis-driven programs which could improve the global ambition of the project”

Several molecular hypotheses are raised in our research project. Some of them concern the involvement of the immune/inflammation system, as shown in our recent publications and data. However, we planned to perform –omic studies to identify some other relevant pathways we can focus on in the future.

3) “Aging of researchers with the most significant expertise in specific experimental domains”

We are aware that the team needs to attract new researchers. This can be hardly done at the moment due to the difficulty to maintain full-time researchers (from Inserm and CNRS) in a University-associated research unit. We have identified some researchers that could be interested to join our program but institutional decisions hampered this process.

Our attractivity would increase, thanks to the great translational program we develop and if we success in having the support of Inserm.

Pr Anne-Dominique Lajoix
Directeur