SOPAM - Stress oxydant et pathologies métaboliques

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Stress Oxydant et Pathologies Métaboliques

Oxidative stress and Metabolic Diseases

(SOPAM)

From the

University of Angers

INSERM

December 2010

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

Section des Unités de recherche

AERES report on the research unit

Stress Oxydant et Pathologies Métaboliques

Oxidative stress and Metabolic Diseases

(SOPAM)

From the

University of Angers

INSERM

Le Président de l'AERES

Didier Houssin

Section des unités de recherche

Le Directeur

Pierre Glorieux

December 2010

Research Unit

Name of the research unit: Stress Oxydant et Pathologies Métaboliques (SOPAM) – Oxidative stress and Metabolic Diseases

Requested label: UMR_S INSERM

N° in the case of renewal:

Name of the director: Mr Ramaroson ANDRIANTSITOHAINA

Members of the review committee

Committee chairman:

Ms. Anne NEGRE-SALVAYRE, University Toulouse 3, Toulouse

Other committee members:

Ms. Muriel LAFFARGUE, University of Toulouse 3, Toulouse

Mr Roger MARTHAN, University Bordeaux 2, Bordeaux

Mr Gerard NASH, University of Birmingham, Birmingham, UK

Mr Ed RAINGER, University of Birmingham, Birmingham, UK (not present)

Mr Jean-Louis GUEAND, University of Nancy (CSS Inserm representative) (not present)

Observers

AERES scientific advisor

Mr Paul HOFMAN

University, School and Research Organization representatives

Mr Raymond BAZIN, INSERM

Mr Jean Louis FERRIER, University of Caen

Mr Yvonnick MORICE, CHU d'Angers

Report

1 • Introduction

- Date and execution of the visit

The visit of the committee took place on December 9 th 2010. The work of the team and the project were presented by the team manager during one hour, which was followed by one hour of discussion and by the presentation of posters focused on the different aspects of the team activity. In the afternoon, the Committee met for further discussion on the project outlines.

- History and geographical localization of the research unit, and brief presentation of its field and scientific activities

The UMR INSERM 694 is part of the University of Angers, UFR of Medical Sciences, and is located in the CHU of Angers. The Unit project SOPAM « Oxidative Stress and Metabolic Diseases » implicates academic full time and teaching researchers and clinicians from the current INSERM Unit 694, and from the INSERM Unit U771. The scientific issues developped in the project deal with metabolic and inflamatory diseases and are focused on the metabolic function of mitochondria, the pharmacology of polyphenols, the role of microparticles in endothelial dysfunction and angiogenesis. The project includes the development of new therapeutic strategies in these diseases. As a consequence, the different aspects of the project associate basic fundamental research and clinical studies

- Management team :

Ramaroson ANDRIANTSITOHAINA, Director

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	8	8
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	4
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	4	4
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	2.9	2.9
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	4	
N6: Number of Ph.D. students (Form 2.7 of the application file)	10	
N7: Number of staff members with a HDR or a similar grade	8	9

2 • Overall appreciation on the research unit

• Summary

The scientific project of this Unit is the logical continuation of the work developed by teams from INSERM U694 and UMR CNRS 6214-INSERM U771. The group comprises 4 full-time researchers EPST (2 DR2 INSERM, 1 DR2 CNRS and 1 CR2 INSERM), teacher-researchers and doctoral students. The project proposes a wide range of *in vivo*, *ex vivo* and *in vitro* studies to investigate the links between metabolic syndrome, microparticle formation/dissemination and inflammation. In vivo studies will include patients in two well controlled cohorts suffering from either metabolic syndrom or obstructive sleep apnea, as well as murine models of disease. In vitro studies will use diverse cell culture systems as well as advanced proteomic/genomic analysis systems to probe the research questions. Two aspects related one to the other, with strong valorisation potential are emphasized, on one hand the biological role of microparticles and polyphenols in metabolic and inflammatory diseases, and on the other hand their use as new therapeutical tools for improving the endothelium function and inflammation (newly engineered microparticles, polyphenols as dietary vasculoprotective agents).

The group is very active and publishes extensively, mainly in mid-ranking journals, some articles being published in the best journals in their specialty (Blood, Diabetes, Am J Respir Crit Care Med, Faseb J, Chest, Am J Pathol., STKE). There is also an excellent technology transfer policy (5 patents, a start-up "in preparation", one INSERM contract of interface, one ANR, two PHRC). The originality of thematics, the cross-cutting approaches associating clinical trials, appropriate animal models and basic research are important factors to ascertain the likelihood of the project's success, and should allow the group to succeed at a national and international recognition, and at an outstanding level of publications.

• Strenghts and opportunities

The committee wishes to emphasize:

- The originality of the scientific project
- The strong interaction and complementarity between researchers and clinicians
- The diversification of financial resources
- The attractiveness of the group (arrival of two full-time EPST researchers in the team, presence of many PhD students)
- The efforts of valorisation and translation into clinical studies.

• Weaknesses and threats

The number of themes developed is important for the size of the team, with some potential risks of dispersion. An effort in the prioritization of themes could be done to make clearer the originality and the feasibility of each project (see below specific comments). The presence of experts in mitochondrial function/biogenesis is a great opportunity for working across disciplines, but the management of their integration needs to be clarified. It is not clear how section 3 (environmental toxins) integrates with work on MP and Polyphenols.

The team has a good publications record. Most ‘primary’ author papers are in mid ranking journals (33% with I.F between 2-4 and 40% with I.F 4-10).

• Recommendations

In view of the large number of themes, it is suggested to prioritize the projects and to focus on the most successful subjects, with regard to international competition. It would be worthwhile to publish fewer but more thoroughly constructed studies integrating *in vitro*, *in vivo* and patient studies since the team has now set the tools to do so. It is also suggested to submit to the very top outstanding journals.

- Production results

cf. http://www.aeres-evaluation.fr/IMG/pdf/Criteres_Identification_Ensgts-Chercheurs.pdf

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	7
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	2
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	0.9
A4: Number of HDR granted during the past 4 years	3
A5: Number of PhD granted during the past 4 years	17

3 • Specific comments

- ## Appreciation on the results

Relevance and originality of the research, quality and impact of the results

The group has developed several original themes on oxidative stress and the mitochondrial function. An important part of the work and of the project is focused on the role of microparticles (MPs) in cardiovascular dysfunction occurring during the metabolic syndrome (MS) or in inflammatory diseases such as the "obstructive sleep apnea/hypopnea syndrome" (OSAHS) and intermittent hypoxia. The hypothesis is that Mps may behave as vectors of biological molecules and information between cells, with consequences on mitochondrial respiration, oxidative stress and endothelium function. The team recently reported a correlation between the circulating level of procoagulant Mps and endothelial dysfunction, vascular hyporeactivity and inflammation occurring during MS. Original and innovative therapeutic strategies are developped using engineered MPs carrying either Sonic Hedgehog to ameliorate endothelial function, or PPAR α to promote angiogenesis. The expertise of the team in this field is a strength of the application

Another important research topic is the pharmacology of polyphenols and of their molecular targets, particularly the estrogen receptor ER α which could mediate, in part, the cardiovascular protective effect of these agents. The team leader is a recognized expert in this field.

Besides these projects, the team has a wide expertise in studying the mitochondrial metabolic function, in the presence of environmental toxicants and in pathophysiological conditions such as MS and in cell proliferative processes.

Quality and number of publications, scientific communications, thesis and other outputs

The scientific production of the team is very important (over 170 publications in the period 2006-2010, 60 % internal to the team), mainly in mid-ranking journals (33% with an I.F between 2-4 and 40 % between 4-10), with some articles being published in the best specialty journals (Blood, Diabetes, Am J Respir Crit Care Med, Cancer Res., J. Immunol., Faseb J, Chest, Am J Pathol, STKE). The team also produced 13 book chapters, 23 invited conferences, scientific communications with proceedings in international (18), and national (43) meetings, 6 communications without proceedings, 10 posters and 17 PhD thesis defended between 2006 and 2010.

Quality and stability of partnerships

The team has a strong ability to get regular funding regional (contracts Region and Canceropole Grand Ouest), national (participation in 3 ANR) or international (participation in two European contracts, DIOGENES, DEISA, contract France / FRSQ with Canada), funding from the charity sector (Fondation de France, National League against Cancer), or private sources (LVMH).

- ## Appreciation on the impact, the attractiveness of the research unit and the quality of its links with international, national and local partners

Number and reputation of the awards obtained by staff members, including invitations to international conferences and symposia

The visibility of the group and of the project leader is evidenced by the number of invited conferences at national and international meetings, as well as by the number of oral communications presented by the team members in international (28) or national (49) meetings over the last 4 years. The project leader also co-organized the Congress "New Frontiers in Cardiovascular Research" in Poland, 2008.

The team leader is board member of GRRC, and member of the scientific advisory board of Paris Est. The team members have international visibility in the field of metabolic diseases and mitochondrial regulation and in endocrinology (a team member is president of the French Endocrinology society).

Ability to recruit high levels scientists, post-docs and students, more particularly from abroad

The group has been reinforced by the arrival of two academic INSERM researchers (1 DR2 and 1 CR2). The attractiveness of the team for students is assessed by the presence of 3 post-doc and 7 PhD students, while 17 PhD thesis have been carried out during the period 2006-2010. International scientific exchanges exist with Canada (France/FRSQ Quebec), Italy and Spain.

Ability to raise funds, to successfully apply for competitive funding, and to participate to scientific and industrial clusters

The team has got a strong ability to obtain regular funding, from region (contracts Region Canceropole Grand Ouest), and national (participation in 3 ANR) or international contracts (participation in two European contracts, DIOGENES, DEISA, contract with FRSQ, Canada), as well as grants from Fundations (Fondation de France, National League against Cancer) or from private companies (LVMH).

Participation to international or national scientific networks, existence of stable collaborations with foreign partners

The team participates in two European contracts, DIOGENES, DEISA, and has a contract with FRSQ in Canada.

The concrete results of the research activity and socio-economic partnerships

The group is involved in the development of platforms (SNP Biogenouest, CIMATH). There is an excellent technology transfer policy, with 5 patents, a start-up currently under finalization, a contract of interface INSERM with the CHU (RA), 2 PHRC, 3 ANR.

- Appreciation on the management and life of the research unit

Relevance of the research unit organization, quality of the management and of the communication policy

The organization of the team is efficient in terms of translational research. Clinical researchers are present in the group and strong interactions exist between clinic and fundamental basic researchers. The techniques are controlled and the access to the various platforms is well-organized.

The organization set up seems appropriate, with the existence of a Managing Team Council including the director/project manager, researchers and teacher-researchers, as well as 2 members representing PhD students or post-doc. The council meets once a month.

Relevance of the initiatives aiming at the scientific animation and at the emergence of cutting edge projects

There is a scientific animation organized through meeting 'projects' and a weekly journal club.

Contribution of the research unit staff members to teaching and to the structuration of the research at the local level

Several teacher-researchers of the team are teaching in various disciplines within the Faculties of Medicine, Pharmacy, Sciences, PCEM1, PCEM2, Masters 1 and 2. The group is part of the Faculty of Medicine and the IFR 132 (the team leader is co-director of IFR132) at the University of Angers, and is also part of the CHU (several members of the team have clinical responsibilities).

- Appreciation on the scientific strategy and the project

The existence, relevance and feasability of a long term (4 years) scientific project

The project is the continuation of the previous work, and is subdivided into 4 independent sub-sections. It is planned to evaluate the role of MPs in the triad "Inflammation, cardio-vascular dysfunction and adipocytes" in metabolic syndrome (section 1), and in the obstructive sleep apnea/hypopnea syndrome" (OSAHS) (section 2). These sections include the hypothesis that plasma borne MPs can interact and modify the signalling and functional capacity of cells in the extravascular environment. The team is very skilled in the characterisation of MP origin, their content and their correlation with disease states.

The team expertise in this field is a strength for the application and its feasibility.

The section 3, focused on the consequences of environmental toxicants on mitochondrial function and metabolic diseases, needs justification, as it is not clear how this section integrates with work on MPs and Polyphenols.

In section 4, the applicants plan to develop new therapeutical strategies for metabolic diseases, including engineered MPs and polyphenols. This section is directly linked to the pathophysiological aspects of sections 1 and 2 since it represents a translational aspect. This section is original, well-balanced, and relevant particularly

the part 4.3 on polyphenols which will use *in vitro* models (to determine the effects of polyphenols on adipogenesis and inflammation), mouse models of obesity and diabetes for studying the systemic effects of polyphenols and dietary trials in patients with OSAHS.

More generally, the feasibility looks good, each section appears well suited as a programme of research (except section 3 which needs further justification).

The project presents very original research topics, with high recovery potential. The numbers of themes being important with a risk of dispersion, it is necessary to better define the priorities and the connections between the different sub-projects.

Existence and relevance of a policy for the allocation of ressources

The team has shown a strong ability to obtain regular regional, national and international fundings, from Fundations and from the private sector. A majority of PhD students have research funding from the MESR.

Originality and existence of cutting edge projects

The development of engineered MPs carrying sonic Hedgehog or PPAR¤ as new therapeutical tools for improving endothelial function and angiogenesis, is particularly original and should allow the group to access at an outstanding level of publications. Studies on the mechanism of action of reservatol and plant polyphenols and the role of the estrogen receptor are novel, and offer the possibility to develop new therapeutic agents.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
STRESS OXYDANT ET PATHOLOGIES MÉTABOLIQUES (SOPAM)	A	A	A	A	A

C1 Qualité scientifique et production
C2 Rayonnement et attractivité, intégration dans l'environnement
C3 Gouvernance et vie du laboratoire
C4 Stratégie et projet scientifique

Statistiques de notes globales par domaines scientifiques

(État au 06/05/2011)

Sciences du Vivant et Environnement

Note globale	SVE1_LS1_LS2	SVE1_LS3	SVE1_LS4	SVE1_LS5	SVE1_LS6	SVE1_LS7	SVE2 _LS3 *	SVE2_LS8 *	SVE2_LS9 *	Total
A+	7	3	1	4	7	6		2		30
A	27	1	13	20	21	26	2	12	23	145
B	6	1	6	2	8	23	3	3	6	58
C	1					4				5
Non noté	1									1
Total	**42**	**5**	**20**	**26**	**36**	**59**	**5**	**17**	**29**	**239**
A+	16,7%	60,0%	5,0%	15,4%	19,4%	10,2%		11,8%		12,6%
A	64,3%	20,0%	65,0%	76,9%	58,3%	44,1%	40,0%	70,6%	79,3%	60,7%
B	14,3%	20,0%	30,0%	7,7%	22,2%	39,0%	60,0%	17,6%	20,7%	24,3%
C	2,4%					6,8%				2,1%
Non noté	2,4%									0,4%
Total	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

*** les résultats SVE2 ne sont pas définitifs au 06/05/2011.**

Intitulés des domaines scientifiques

Sciences du Vivant et Environnement

• SVE1 Biologie, santé
- **SVE1_LS1 Biologie moléculaire, Biologie structurale, Biochimie**
- **SVE1_LS2 Génétique, Génomique, Bioinformatique, Biologie des systèmes**
- **SVE1_LS3 Biologie cellulaire, Biologie du développement animal**
- **SVE1_LS4 Physiologie, Physiopathologie, Endocrinologie**
- **SVE1_LS5 Neurosciences**
- **SVE1_LS6 Immunologie, Infectiologie**
- **SVE1_LS7 Recherche clinique, Santé publique**

• SVE2 Ecologie, environnement
- **SVE2_LS8 Evolution, Ecologie, Biologie de l'environnement**
- **SVE2_LS9 Sciences et technologies du vivant, Biotechnologie**
- **SVE2_LS3 Biologie cellulaire, Biologie du développement végétal**

INSERM UMR U. 694

Université d'Angers
Bâtiment IHURIS
Rue des Capucins
49100 – ANGERS Cedex

Ramaroson ANDRIANTSITOHAINA
Directeur de Recherche INSERM
Porteur du Projet « SOPAM »

SOPAM « Stress Oxydant et Pathologies Métaboliques »
Observations de portée générale sur le rapport dévaluation

L'ensemble des membres de l'Unité et le porteur du projet remercient le comité de visite pour leur travail et leur rapport.

Nous avons noté avec grand intérêt et satisfaction les commentaires positifs rapportés dans cette évaluation, et tout particulièrement l'originalité du projet scientifique, les relations étroites et complémentaires entre les chercheurs et les cliniciens, la diversification des ressources financières, l'attractivité du groupe ainsi que les efforts de valorisations et le caractère translationnel de la recherche qui est mené. Nous avons également noté les évaluations positives sur la gouvernance.

Nous avons apprécié les commentaires du comité sur les points forts de nos recherches concernant l'évaluation du rôle des microparticules en tant que marqueurs et vecteurs d'informations biologiques dans les pathologies comme le syndrome métabolique et le syndrome d'apnée du sommeil et les stratégies développées pour lutter contre celles-ci par l'ingénierie des microparticules elles-mêmes et par les polyphénols végétaux.

Concernant les points à améliorer :

- la priorisation des projets au regard de la compétition internationale :

  Malgré un effort de recentrage réalisé sur la fusion de deux équipes ayant deux thématiques différentes et complémentaires, nous sommes conscients de la difficulté qui persiste et notamment les notions d'homogénéité thématique et l'imbrication entre la partie concernant les toxiques environnementaux et les travaux menés sur les microparticules et les polyphénols. Cet effort qui s'est poursuivi au sein de l'unité depuis le dépôt du dossier converge avec les recommandations du comité de visite. Ainsi, nous allons prioriser nos thématiques de recherches en développant principalement les points forts du projet concernant le rôle des microparticules dans la triade « inflammation, dysfonction cardio-vasculaire et adipocytes dans le syndrome métabolique, et au cours du syndrome d'apnées du sommeil. Un intérêt particulier portera sur le rôle et la participation de la mitochondrie dans ces pathologies en tenant compte l'expertise des membres de l'unité sur le sujet. Il sera également mis en avant les recherches sur les stratégies thérapeutiques pour lutter contres les effets délétères de ces pathologies au travers du développement des microparticules en tant que vecteurs molécules protectrices et de nos connaissances sur les polyphénols végétaux. Au travers de ces recherches, le but est de proposer des pistes de diagnostiques et thérapeutiques par une double approche mettant en jeu les nutriments et les médicaments.

Concernant l'impact de petites molécules contaminantes de l'environnement sur les fonctions mitochondriales et les conséquences induites sur les régulations métaboliques cellulaires, le but est de vérifier l'hypothèse selon laquelle les perturbations métaboliques peuvent expliquer en partie les pathologies de stockage. Il s'agit ici d'un pari scientifique et le développement de cette thématique dépendra de l'évolution des résultats très intéressants obtenus récemment et de la capacité de l'équipe à s'étoffer au cours du prochain contrat en potentiel humain.

L'ensemble de ces critères nous emmène à concentrer principalement nos efforts sur les points forts mentionnés par le comité de visite.

- Malgré un grand nombre de publication dans les meilleurs journaux de spécialités et des journaux de visibilité moyenne, il est recommandé d'augmenter le nombre de publications dans des journaux à très haut facteur d'impact et de journaux généralistes :

Nous avons maintenant mis en place les protocoles de recherche translationnelle et de recherche clinique avec des cohortes bien établies et des approches fondamentales pluridisciplinaires qui abordent l'ensemble des échelles du vivant du moléculaire à l'animal entier. La mise en commun de ces compétences augmentera le potentiel de l'Unité à publier dans des « top outsanding journals ». Nous allons concentrer notre effort pour arriver à ce but au cours du quinquennal à venir.