Hypoxie : physiopathologie cardiovasculaire et respiratoire

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Hypoxia, Patho-Physiology

From the

University Grenoble 1

INSERM

May 2010

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INSERM

Le Président de l'AERES	Section des unités de recherche
	Le Directeur
Jean-François Dhainaut	**Pierre Glorieux**

May 2010

Research Unit

Name of the research unit: Hypoxia, patho-physiology

Requested label: UMR_S INSERM

N° in the case of renewal:

Name of the director: M. Patrick LEVY

Members of the review committee

Chairperson:

M. Jean Claude WILLER, University Paris 6

Other committee members:

M. Serge ADNOT, University Paris Est Créteil

M. Richard SCHULTZ, University of Giessen Lung Center, Germany

Ms. Lena LAVIE,Technion Institute of Technology, Haifa, Israel

M. Bengt KAYSER, University of Geneva, Switzerland

Committee members nomminated by staff evaluation committees (CNU, CoNRS, INSERM and INRA CSS....)

M. Jean Claude WILLER, Paris, CNU member

Ms Chantal BOULANGER, Paris, INSERM CSS member

Observers

AERES scientific advisor:

M. Bernard LEVY

University or School representatives:

M. Hervé PELLOUX

Research Organization representatives:

M. Raymond BAZIN, INSERM

M. Patrice MARCHE, INSERM

Report

1 • Introduction

- Date and execution of the visit:

The evaluation and site visit were organized in the University Joseph Fourier, Grenoble on february 8th 2010. Due to problems of transportation for several experts, the visit started by a laboratory visit later than expected. The scientific program was well-organized and respected ; the experts obtained, from the director and from the team members, all detailed and informed responses to their questions.

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

This unit has been created in 2002. It originated from two laboratories (LSCPA, J De Leiris, director and PRETA, P Lévy director, part of TimC UMR CNRS 5525). The laboratory has been established since its creation in the Jean Roget Institute building (6th floor). The laboratory as well as the technical facilities (animal housing) has been fully renewed in 2004. The laboratory has been certified by Inserm in 2005 for 3 years (ESPRI) and re-certified for 4 years in 2007 (ESPRI). The research is centered on the cardiovascular consequences of sleep apnea, from basic mechanisms to clinical applications including therapeutic trials, the scientific strategy combining experimental (i.e. animal models) and clinical approaches.

- Management team:

Patrick Levy (Director) and Christophe Ribuot (Assistant 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)	13	16
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3	6
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3	3
N5: Number of other engineers, technicians and administrative staff (Form 2.6 of the application file)	4*	4*
N6: Number of Ph.D. students (Form 2.7 of the application file)	8	7
N7: Number of staff members with a HDR or a similar grade	10	11

*4 clinical research assisitants participate to the project

- Data on the work produced:

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

A1: Number of permanent researchers with or without teaching duties (recorded in N1 and N2) who are active in research	18
A2: Number of other researchers (recorded in N3, N4 and N5) who are active in research	6
A3: Ratio of members who are active in research among permanent researchers [(A1)/(N1 + N2)]	100%
A4: Number of HDR granted during the past 4 years	3
A5: Number of PhD granted during the past 4 years A6: Any other relevant item in the field	8

2 • Detailed Appreciation

- Appreciation on the results:

The director of the Unit and the researchers of the team are clearly leaders in their fields. The combination of fundamental and applied research has put them and continues to place them in a unique position to advance the area's of cardiovascular complications of obstructive sleep apnea (OSA) from both the technological and conceptual points of view. Ongoing focus on OSA and hypoxia has been the strength of the unit, the impact on the broader field of vascular biology and the integrated response to hypoxia has been enhanced by approaching vascular complications of OSA in a broader sense and in a broader variety of conditions including and physical inactivity.

The team is considered by the experts of the visit as a leading european group dealing with intermittent hypoxia in human and animal models. The research is considered of high relevance given the high prevalence of OSA, obesity and physical inactivity.

One originality of the group not shared by most of the other european group in this field of research is the combination of experimental (i.e. animal models) and clinical approaches, with the recent development of a unique human model of long-term intermittent hypoxia in healthy subjects. The impact of the research is also visible in terms of treatment strategies aimed at reducing the cardiovascular complications of OSA or intermittent hypoxia.

The team members are the authors of more than 90 publications since 2005. Most of them have been done in the lab. Six of them have been published in high-ranking journals, including Circulation, American Journal of Respiratory and Critical Care Medicine, and *Journal of Allergy and Clinical Immunology*, during the last three years. One general impression of the committee is that the quality of the publications is improving and should reach an outstanding level in the next future.

The team has trained 8 PhD students in the past 5 years for 11 HDRs which allows a good quality of supervision.

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

The director of the Unit is a well–recognized scientist with a leadership in the field of OSA. The Unit has a good visibility in Europe and USA, and was considered by the experts of the committee as belonging to the top 10 in research on OSA worldwide. The is illustrated by the fact that the Unit recruited two young scientists during the last 4 years, recently appointed by the INSERM as CR2. One PhD student of the unit is from abroad.

The national and international visibility of this team is indisputable. They participated actively in international meetings (invited lectures), The director is vice-chair of a European Consortium (COST B26: sleep apnea and cardiovascular) (2007-2010), and he has been the recipient of the Actelion AREA award (2007).

The unit director is associate editor of recognized medical journals (European Respiratory Journal, Journal of Sleep Research and Sleep Medicine).

As mentioned above, the Unit recruited two young scientists during the last 4 years, recently appointed by the INSERM as CR2. One PhD student of the unit is from abroad.

The team obtained during the last 4 years a large number of grants (PHRC, INSERM-DHOS translational research grants…) and private contracts and participated actively in international projects. P Levy is the European leader or the coordinator of several clinical trials supported by drug companies.

The set up for exposure to intermittent hypoxia in healthy subjects has been developed in close collaboration with a US team (Harvard, Boston), with studies conducted in collaboration.

The team has good relationships with pharmaceutical companies and technological companies. One patent on non-invasive ventilation technology has been registered.

- Appreciation on the strategy, governance and life of the research unit:

The balance between fundamental and applied research is adequate and an example for other groups. There is a good interaction between the hospital and laboratory activities at the level of the senior investigators, and a good communication between seniors and students of the team. The PhD students specifically declared their entire satisfaction with the supervision by the senior researchers, although they wish a closer interaction between fundamental and clinical teams. The technical staff, even though slightly worried by the suboptimal workload to staff ration, also expressed their entire satisfaction with the supervision by the senior scientists also underlining the adequate material environment for their daily work.

There is a good equilibrium between fundamental and applied research, in particular regarding translationnal projects related to cardiovascular complications of intermittent hypoxia (identification of subclinical markers and of biomarkers, validation of new pharmacological targets, new drug trials, role of OSA on non arteritic ischemic optic neuropathy ...). Tools have been developed to specifically investigate the underlying mechanims of cardiac and vascular remodeling during conditions of intermittent hypoxia, in both rodents and humans, taking into account comorbities such as obesity, systemic hypertension, or atherosclerosis . This is also illustrated by the project on adipose tissues and its role in inflammation under conditions of hypoxia and exercise.

Regarding university formation, the Unit members are involved in several Masters. They have trained 7 PhD students in the past 5 years for 11 HDR which allows a good quality of supervision.

The Unit is very well integrated in the campus and very well considered by the University representatives.

- Appreciation on the project:

Built on previously published data, the new project is clearly innovative and creative and will most likely be as productive as in the recent past, with similar high impact for the scientific community. The productivity of the research is also guarenteed by the recent recruitment of two young CR2 INSERM researchers who will bring and develop their expertise in molecular, cellular and integrative biology, and in the development of innovative experimental models.

The new project is focused on underlying mechanisms and therapeutic options for OSA, including investigation of molecular factors identified during the last years (inflammatory cytokines, CCR5, HIF-1, adipokinins, leukotriens) and drug trials targeting specific factors involved in systemic hypertension and cardiovascular complications of OSA. A new research orientation will concern the interaction between adipose tissue and vascular remodeling which will be investigated clinically and experimentally. Another new aspect concerns the consequences of OSA on muscle function and trophicity.

The development of the new project is also guaranteed by a good level of financing. Staffing appears sufficient with regard to the number and specialties of the researches and the Unit has considerable attractiveness for PhD students.

The committee however draws the attention to the fact that the technical staff seems undersized and that one full time technician with major responsibilities is retiring in 2010. In order for the project to be realised in optimal

conditions the committee considers it of utmost importance to strengthen the technical staff by replacing the retiring technician and completing with an additional technician.

Two aspects of the Unit can be considered original and involve some risk taking. Firstly the resolute translational approach covering the whole spectrum of experimental approaches from bench to bed side combining molecular, cellular, transgenic and clinical experiments all around the main thematics of interest of the Unit. Second, the strategy to include physical activity and obesity related parameters into their research endeavour which is highly relevant from a public health perspective but also increases the complexity of their work. The committee finds this initiative bold but realistic and certainly extremely relevant.

- Conclusion:

  - Overall appreciation:

The committee judges this unit to rank within the top 15 to top 5% of their respective area's of expertise worldwide. The dossier and the various aspects presented during the visit offer a highly coherent and dedicated research structure. Original approaches and ideas guarantee the individuality of the Unit and an expected progression to an outstanding level. The Unit is internationally respected and participates in international cooperative projects. The visibility of the senior scientists on the international research arena is high. The long-term viability of the Unit seems to be very well prepared and the clear plans and the clear commitment of the local authorities, makes the future look bright.

  - Strengths and opportunities:

One major strength of the group is to combine fundamental and applied research. The comity found that the research quality of the Unit was continuously improving with an increasing expertise in molecular, cellular and integrative biology, and with the development of innovative experimental models and human studies. The young scientists recently recruited should be encouraged to take risk in developing research based on innovative experimental models, in synergy with the clinical research approach.

  - Weaknesses and threats:

The numerous potential confounding factors resulting from the association of OSA with obesity; this might complicate the identification of relevant molecular mechanisms and lead to the publication of descriptive rather than mechanistic studies.

The lack of recognized "in-house" expertise on obesity and adipocyte function and regulation, may jeopardize the impact of future publications.

The sub-project on HIF-1-alpha activation under conditions of intermittent hypoxia has a relatively narrow focus on the role played by endothelin. It is suggested that the investigators expand their experiments to other vasoactive mediators known to be induced by HIF-1-alpha such as VEGF and adrenomedullin.

In general the number and nature of the scientific output is very good but with still some room for improvement. Taking into account the ambition and the quality of the research, this unit should be able to reach very high impact journals out of the specialty area.

  - Recommendations

The Clinical Research done by the team is judged excellent and there is no question that it should continue at the same level in the next future. Based on the original approaches and ideas developed by this team, there is a room for improvement of the research based on innovative experimental models, in synergy with the clinical studies. In addition, the group should initiate close collaborations with teams with international recognized expertise in obesity and adipocyte function.

Note de l'unité	Qualité scientifique et production	Rayonnement et attractivité, intégration dans l'environnement	Stratégie, gouvernance et vie du laboratoire	Appréciation du projet
A	A	B	A	A

PRESIDENCE

UNIVERSITE JOSEPH FOURIER
SCIENCES.TECHNOLOGIE.SANTÉ.
GRENOBLE 1

Nos Réf. LD/GG/FT 189 -10
Tél. 04 76 51 48 29 - Fax 04 76 51 43 12

Grenoble, March 16th 2010,

AERES
Mr. Jean François Dhainaut

Subject : Comments of University Joseph Fourier Grenoble 1 on AERES preliminary report
Hypoxia, patho-physiology - EA 3745 / ERI 17 – Head : Pr. Patrick LEVY

Mr. Chairman of the visiting committee, Dear Colleague,

We have examined the preliminary assessment report dated March 4th 2010 for research unit :
Hypoxia, patho-physiology - EA 3745 – ERI 17
On behalf of the University and all members of this laboratory, we would like to express our thanks for this thorough assessment.

We would also like to emphasize some of the detailed comments that have been provided by the committee and to answer to the raised issues.

1) We are very pleased of the overall evaluation of the scientific production, the impact and attractivity of our research unit. Being evaluated as belonging to the top 10 of the OSA research worldwide is very positive. Similarly, being ranked in the top 5-15% of the respective areas of scientific expertise worldwide of the committee is very satisfactory.

2) We would also like to acknowledge that the committee evaluates that the long-term viability of the Unit has been very well prepared and is fully supported by the University authorities. From this perspective, we are particularly pleased that the integration of the exercise research group (Rex-S) which allows "*to include physical activity ad obesity related parameters into their research endeavor which is highly relevant from a public health perspective but also increases the complexity of the work*" has been positively evaluated. The committee also "*finds this initiative bold but realistic and certainly extremely relevant*".

3) We also very much appreciate that the committee evaluated that "*the major strength of the group is to combine fundamental and applied research*" and that "*the unit was continuously improving with an increasing expertise in molecular, cellular and integrative biology and with the development of innovative experimental models and human studies*".

4) In response to the weaknesses and threats that have been pointed out by the committee:

a. We agree on the possible complexity issued from the numerous confounding factors resulting from the association between obesity and OSA. In order to adequately dissect the molecular mechanisms that are involved, we have chosen a strategy that either limits the contribution of adiposity (normal volunteers, rodents) or alternatively enhances its possible role (obese OSA, Obesity Hypoventilation Syndrome, Apo E-/- mice, Zucker rats). It seems that the comparison between these different models should be highly valuable in an attempt to delineate the specific contribution of the adipose tissue and its interaction with intermittent hypoxia. This is specifically why we planned to analyze in great details the morphologic, functional and cellular changes of the adipose tissue occurring in response to apneas and/or intermittent hypoxia in patients, normal

volunteers and rodents. This is currently being performed in association with experts in the field (see point b).

b. We acknowledge that there is currently limited in-house expertise on fundamental mechanisms of obesity and adipocyte function and regulation. However, although we may have insufficiently mentioned that during the visit, we very much anticipated this limitation and implemented more than 18 months ago a very close scientific cooperation with two leading teams in the field (Jennifer Rieusset (INSERM U870/ INRA 1235, Hubert Vidal, Lyon) and Louis Casteilla (UMR 5241 CNRS, Toulouse)). This already led to several animal experiments with both teams and there is a clinical research program (ADISAS) starting that includes Martine Laville (CERNH, Lyon) and Jennifer Rieusset with respect to metabolic evaluation and adipose tissue biology. In addition, a young researcher, focused on obesity, (Anne-Laure Borel) currently in post-doc in JP Després's laboratory (Laval University, Quebec, Canada) will join our lab. She has already been included in our research activity (AL Borel, Diabetes Care, 2009) and will promote close cooperation with JP Després, a world leader in the field.

c. We do agree with the committee that the focus of the sub-project on HIF-1α should be enlarged and not only centered on endothelin. We are interested in uncovering HIF-1 target genes involved in the development of the cardiovascular complications of intermittent hypoxia and OSA. This is why we have proposed to look at NHE1 and PPARy, both known to have adverse cardiac actions. VEGF and adrenomedullin, as well as angiopoietin, are protective HIF-1 target genes and are known to be increased in OSA patients possibly to counteract OSA-related cardiovascular effects. In this respect, we have unpublished data showing that VEGF and cardiac angiogenesis are increased in our intermittent hypoxia rat model. However this is not sufficient to prevent the increased sensitivity to myocardial ischemia brought about by chronic exposure to intermittent hypoxia. It could however be interesting to evaluate whether activation of these genes does indeed limit this deleterious response.

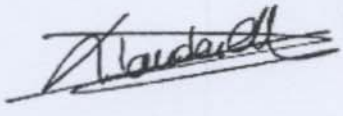
5) We agree with the objective put forward by the committee in terms of very high level of publication in journals out the specialty area.

Besides, you will find enclosed in a separate document, some additional comments related to technical inaccuracies.

Yours faithfully.

P/ Le Président de
l'Université Joseph Fourier Grenoble I
Farid OUABDESSELAM

P/O Le Vice-président
du Conseil Scientifique de
l'Université Joseph Fourier Grenoble I
Laurent DAUDEVILLE



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Faculté de Médecine – Faculté de Pharmacie
de Grenoble

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Grenoble, March 16th 2010

Comments on AERES preliminary report
EVAL-0381838S-S2110044039-UR-RPRELIM LEVY.doc

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