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## HP2 - Hypoxie physiopathologie

Rapport Hcéres

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# HCERES

High Council for the Evaluation of Research  
and Higher Education

Research units

HCERES report on research unit:

Hypoxie PhysioPathologie

HP2

Under the supervision of  
the following institutions  
and research bodies:

Université Joseph Fourier - Grenoble - UJF

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

# HCERES

High Council for the Evaluation of Research  
and Higher Education

Research units

*In the name of HCERES,<sup>1</sup>*

Didier HOUSSIN, president

*In the name of the experts committee,<sup>2</sup>*

Laurent NICOD, chairman of the committee

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Under the decree N<sup>o</sup>2014-1365 dated 14 november 2014,

<sup>1</sup> The president of HCERES "countersigns the evaluation reports set up by the experts committees and signed by their chairman." (Article 8, paragraph 5)

<sup>2</sup> The evaluation reports "are signed by the chairman of the expert committee". (Article 11, paragraph 2)

# Evaluation report

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

Unit name:	Hypoxie PhysioPathologie
Unit acronym:	HP2
Label requested:	INSERM
Present no.:	U1042
Name of Director (2014-2015):	Mr Patrick LEVY
Name of Project Leader (2016-2020):	Mr Jean-Louis PÉPIN

## Expert committee members

Chair:	Mr Laurent NICOD, Centre Hospitalier Universitaire Vaudois, Switzerland
Experts:	Ms Marie-Christine ALESSI (représentante des CSS INSERM) Mr Konrad BLOCH, UniversitätsSpital Zürich, Switzerland Ms Geneviève DERUMEAUX, représentante du CNU Mr Raphaël HEINZER, Centre d'Investigation et de Recherche sur le Sommeil, Switzerland

### Scientific delegate representing the HCERES:

Mr Patrick LACOLLEY

### Representatives of the unit's supervising institutions and bodies:

Mr Jean-Luc BOSSON, Joseph Fourier University  
Ms Chantal LASSERRE, INSERM

## 1 • Introduction

### History and geographical location of the unit

The HP2 laboratory has been created in 2001 to develop an original research project addressing adverse cardiovascular and metabolic consequences of intermittent hypoxia and sleep apnea, using both animal models and innovative clinical research.

For the past 5 years the structure of the laboratory and its scientific project have been based on 4 groups 2 in animal research (one on Vascular remodelling and atherosclerosis and one on Adaptation to chronic intermittent hypoxia: HIF-1 and its target genes, both located on the 6th floor of the Jean Roget Building, medical faculty campus, Grenoble University) and 2 in translational and clinical research (one on sleep apnea and hypoxia, and the other on exercise and hypoxia located in the Hôpital Michallon and the Hôpital Sud, respectively).

Both animal and clinical research was supported through active cooperation with various French INSERM and CNRS teams (INSERM U870/ INRA 1235 Lyon, UMR 5241 CNRS Toulouse, Institute of Cardiometabolism and Nutrition, Pitié-Salpêtrière Hospital, Paris and INSERM U872, INSERM U1063 in Angers as well as local and international cooperation

The HP2 laboratory will be one of the main cornerstones of the *CReSi Center for integrative health* a core project of University Grenoble-Alpes in the coming years. This center will promote cross-disciplinary approaches and innovative technologies for both the healthy ageing population and chronic diseases including sleep apnea

### Management team

The former director is Mr Patrick LEVY and the future director is Mr Jean-Louis PEPIN.

There are three subteams: 1) Preclinical team; 2) Clinical and Translational research team: Intermittent Hypoxia and Sleep Apnea; 3) Exercise-Hypoxia team

### HCERES nomenclature

SVE1\_LS4

### Unit workforce

Unit workforce	Number as at 30/06/2014	Number as at 01/01/2016
<b>N1:</b> Permanent professors and similar positions	22	25
<b>N2:</b> Permanent researchers from Institutions and similar positions	2	2
<b>N3:</b> Other permanent staff (without research duties)	6	6
<b>N4:</b> Other professors (Emeritus Professor, on-contract Professor, etc.)	1	1
<b>N5:</b> Other researchers (Emeritus Research Director, Postdoctoral students, visitors, etc.)	4	4
<b>N6:</b> Other contractual staff (without research duties)	12	11
<b>TOTAL N1 to N6</b>	<b>45</b>	<b>47</b>

Unit workforce	Number as at 30/06/2014	Number as at 01/01/2016
Doctoral students	11	
Theses defended	16	
Postdoctoral students having spent at least 12 months in the unit	1	
Number of Research Supervisor Qualifications (HDR) taken	4	
Qualified research supervisors (with an HDR) or similar positions	19	26

## 2 • Overall assessment of the unit

### Global assessment of the unit

This unit is an outstanding translational program on Sleep disorders and related intermittent hypoxia. They focused their research on cardiovascular diseases and on the metabolism disorders after sleep disturbance and intermittent hypoxia. Their research is based on novel cell studies, unique and strong murine models and cutting edge clinical tools. Their findings have societal impact due to the high proportion of inhabitants afflicted by sleep apnea and obesity. They are highly supported by the industry which is eager to use new devices and is willing to value several patents. They have developed website for patient education in the presence of sleep disorders and created rehabilitation programs based on knowledge developed on the benefits of exercise and of exposure to hypoxia.

Their translational research is attractive and has allowed the emergence of very talented young principal investigators (two of them from INSERM) and the arrival of doctorants and post-doctorants including 3 of them from abroad coming with their own resources. They have received remarkable public and private fundings which are well deserved and will allow to expand their program and exploit results .

The future is promising with not only strong research background but also the arrival young researchers with very structuring projects supported by their university and by national and international collaborations where they have leader positions. The creation of a new platform CReSI center for integrative health, a core project of the University Grenoble-Alpes will allow to give the best environment for basic sciences to unravel physiopathologic mechanisms involved in major chronic diseases some of which are chaired in Cancer genesis.

### Strengths and opportunities in relation to the context

This group has built a unique entity addressing adverse cardiovascular and metabolic consequences of intermittent hypoxia and sleep apnea, using both in vitro models, unique murine approaches and innovative clinical research.

They are part of prospective observational cohorts, with phenotyping and biobanking of non obese and other wise healthy patients with obstructive sleep apnea cohort addressing the specific impact of intermittent hypoxia without confounders. This is unique in the field. The "Observatoire Sommeil de la Fédération Française de Pneumologie (OSFP)" is the largest registry in the world with more than 80.0000 patients lead by this team of Grenoble. Biobanking in at least 3 projects should help to further define personalized therapeutic strategies to avoid systemic and vascular inflammation or non alcoholic fatty liver disease.

The clinical and transitional exercise team has developed new tools to quantify microvascular function in healthy subjects and in physiopathological setting to allow pharmacologic studies on microvascular dysfunction related to sleep apnea. One of these tools is a choroid and optic nerve head blood flow analysis by laser doppler flowmetry prototype. This preclinical team cover three main topics related to intermittent hypoxia on vascular remodeling, cardiovascular and their metabolic consequences with elaborated basic biologic approaches. Among the metabolic pathways the role of leukotrienes, the stress of endoplasmic reticulum and of oxidative stress are the most successful and promising for new therapeutic approaches.

The exercise-hypoxia team show a strong new impetus. Powerful tools such as magnetic resonance imaging or transcranial magnetic stimulation have been implemented into a platform to provide exhaustive and integrated evaluation of cardiometabolic and neuromuscular functions. These tools are used to see how exercise training can impact cardiovascular and metabolic status in various patient population such as chronic obstructive pulmonary disease (COPD), obese patients or rheumatic diseases. Similarities between hypoxic pathways in these later diseases and the hypoxic environment of tumor is of great promise.

The socio-cultural impact is already obvious for the prevention of cardiovascular diseases and metabolic disorders related to sleep diseases. With patient organisations telemetric projects have been built and teaching program organised part of which are website based.

The organisation of the unit has been strengthened lately with the emergence of new team leaders recognised internationally and highly appreciated by doctorants and post-doctorants recruited in greater number. The three groups meet on a regular rhythm and exchanges occur despite dispersion of sites between the south and north of Grenoble.

The impact on the academic community is clear with more than 210 publications since 2011, a large number of invitations internationally. The group has shown himself attractive for young scientists but also for phase 1 and 2 trials in pharmacologic developments, and is remarkable for the use of new tools and depositions of promising patents to correct apneas for instance.

The scientific strategy is excellent with many complementarities in the research from cell biology, murine model and clinical studies either in hypoxic environment, hypoxic diseases or during exercise. The similarities between hypoxic conditions and the tumors open new venues. The new platform CReSI center for integrative health, a project of the University Grenoble-Alpes will allow to involve further basic sciences to facilitate even further translational research.

#### Weaknesses and threats related to the context

The presence of the group on two campus (north and south) is an handicap which is been overwhelmed by regular meetings from the PhD students and researchers. The transition of director will need a close coordination of projects to facilitate further in depth research and focus on mechanisms . The young rising team leaders will facilitate these approaches and exchanges

The number of full time INSERM researchers needs to be increased.

There is a lack of sufficient technical staff especially for animal experiments.

#### Recommendations

The translational approach of sleep disorders and intermittent hypoxia makes this unit a leader in the field. They have established unique models to try to unravel physiopathologic pathways further in depth. There are opportunities to build on actual cohorts, to further define biomarkers and new therapeutic targets. In this regard omics, in particular proteomics or metabolomics could open great opportunities.