HCERES

High Council for the Evaluation of Research and Higher Education

Research units

HCERES report on research unit:

Translational Gene Therapy for neuromuscular and retinal diseases

Under the supervision of the following institutions and research bodies:

Université de Nantes

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

Evaluation Campaign 2015-2016 (Group B)

HCERES

High Council for the Evaluation of Research and Higher Education

Research units

In the name of HCERES,[1]

Michel COSNARD, president

In the name of the experts committee,[2]

Roger LE GRAND, chairman of the committee

Under the decree No.2014-1365 dated 14 november 2014,

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

[2] The evaluation reports "are signed by the chairman of the expert committee". (Article 11, paragraph 2)

Evaluation report

This report is the sole result of evaluation by the expert committee, the composition of which is specified below.

The assessments contained herein are the expression of an independent and collegial reviewing by the committee.

Unit name:	Translational Gene Therapy for neuromuscular and retinal diseases
Unit acronym:	
Label requested:	UMR
Current number:	1089
Name of Director (2015-2016):	Mr Philippe MOULLIER
Name of Project Leader (2017-2021):	Ms Oumeya ADJALI

Expert committee members

Chair:	Mr Roger LE GRAND, CEA-INSERM - Université Paris Sud
Experts:	Mr François TROTTEIN, Centre d'infection et d'immunité de Lille, Université de Lille
	Ms Els VERHOEYEN, CIRI Lyon, ENS, Université de Lyon (representative of the INSERM CSS)
Scientific delegate representing the HCERES:	Mr Jacques NOËL
Representatives of supervising institutions and bodies:	Mr Fréderic BENHAMOU, Université de Nantes
	Ms Chantal LASSERRE, INSERM
Head of Doctoral School:	Ms Corinne MIRAL, Doctoral School n° 502 "Biologie Santé"

1 • Introduction

History and geographical location of the unit

The INSERM UMR 1089 “translational gene therapy for neuromuscular and retinal diseases” is located in the “Institut de Recherche en Santé de l'Université de Nantes” (IRS-UN), in Nantes. The unit was created in January 2011 with the goal to develop translational research programs for gene therapy of neuromuscular and retinal genetic diseases, up to Phase I/II and III clinical trials. The program is based on the expertise developed by the team since 1996, particularly reinforced since 2004 by the development of recombinant Adeno-Associated Virus (rAAV)-derived vectors.

The unit has also implemented the “Centre de Production des Vecteurs” (CPV, Nantes University Hospital), a preclinical manufacturing facility, as well as a GMP-compliant unit (Atlantic BioGMP, EFS) to have direct access to preclinical as well as clinical rAAV vector batches. The unit conceived and organized the animal facility of the “Boisbonne gene and cell therapy center” located at ONIRIS veterinary school, for preclinical evaluation of candidate products in large animal models.

In addition, the unit has access to several on site technological core facilities hosted by the "Structure Fédérative de Recherche" (SFR) Mr François BONAMY (high throughput sequencing, bioinformatics, cell sorting and flow cytometry, cell and tissue imaging, cardiac and muscle strength evaluation, animal transgenesis).

Management team

The current director is Mr Philippe MOULLIER. For the next contract Ms Oumeya ADJALI will head the unit.

HCERES nomenclature

SVE1_LS7 Recherche clinique, Santé publique

Scientific domains

The unit is focused on rAAV-based gene therapy of neuromuscular diseases, Duchenne muscular dystrophy (DMD) in particular, and retinal diseases, including Rod-cone dysplasia, retinitis pigmentosa and Stargardt disease…

Preclinical research is developed in core labs, in particular for neuromuscular disease and retinal diseases in dogs and Non-Human Primates (PNH). Rodent models are also in development.

Unit workforce

Unit workforce	Number on 30/06/2015	Number on 01/01/2017
N1: Permanent professors and similar positions	4	4
N2: Permanent researchers from Institutions and similar positions	3	3
N3: Other permanent staff (technicians and administrative personnel)	5	5
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)		
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	6	
N6: Other contractual staff (technicians and administrative personnel)	7	
N7: PhD students	6	
TOTAL N1 to N7	**31**	
Qualified research supervisors (HDR) or similar positions	5	

Unit record	From 01/01/2010 to 30/06/2015
PhD theses defended	6
Postdoctoral scientists having spent at least 12 months in the unit	2
Number of Research Supervisor Qualifications (HDR) obtained during the period	1

2 • Overall assessment of the unit

Introduction

Translational science is the hallmark of the unit, which has a remarkable organization that covers all stages of the development of a gene therapy product, from basic science, vectorology, proof of concept studies in small and large animal models, to clinical trials. To tackle this objective, the unit is organized in four strongly integrated thematic groups on “innovative vectorology”, “gene therapy of neuromuscular diseases”, “gene therapy of retinal diseases” and “Immunology of AAV-based gene transfer”.

Each thematic group has a scientific leader and a dedicated staff. The unit also relies on Core laboratories for Vector Production (CPV), GMP production (Good Manufacturing Practices)(ABG or Atlantic BioGMP) preclinical studies (Boisbonne center) and GCLP monitoring (Good Clinical Laboratory Guidelines) of clinical trials. Projects are conducted under the ISO9001 Quality Assurance (QA) certification.

During the past term, 2011-2015, the unit has continued to strengthen its scientific program in the development of rAAV for gene therapy of neuromuscular and retinal disease. A significant extension of the preclinical research programs in large animal models (dogs and non-human primates, NHP) was undertaken, which was a critical

step for the translation of the therapeutic strategies into clinical trials; in particular a Phase I/II trial for RPE65 deficiency, completed in 2014, is now extended to a second trial scheduled for 2017. A remarkable organization and re-structuring have been undertaken to tackle all the challenges of these translational medicine programs, from basic studies, to vector design, preclinical testing, GMP production and GCLP core labs to monitor clinical phase studies. The recruitment and involvement of young scientists, who are now taking the lead of the programs, have been strongly promoted.

Global assessment of the unit

The unit has made, over the past 5 years, major breakthroughs in several diseases. In particular, they reported the proof of concept of a successful restoration of vision after treatment with rAAV gene therapy products in PDE6ß and RPGRIP-deficient dogs, two large animal models of rod-cone and cone-rod dystrophies. This approach is now being translated into clinical trials (AAV5- PDE6ß) in collaboration with HORAMA (spin off of the unit).

The team has a very good record of scientific production which increased during the past two years, with publications in several good to excellent peer reviewed journals (Molecular Therapy, Human Gene Therapy, Gene Therapy, Nature Medicine…). The international visibility is high, as illustrated by the sustained contribution to international meetings, including as invited speakers and for oral abstract presentations. The partnership with several prestigious institutions illustrates the quality of the established network (Harvard University, TIGET-Milano, Institute of Myology and Holloway College in London, Clinigen EU network of excellence). The level of research contracts (ANR, Genethon, région “Pays de la Loire”) is outstanding.

Altogether, and combined with a quite unique expertise in rAAV vectors developed from basic programs to GMP production and clinical trials, the unit is highly attractive for young investigators of diverse origins who are encouraged to lead some of the key new research programs.

The management and the new organizational chart are structured to foster the translational medicine perspective of the unit’s global project. This certainly explains also the recent successes in patent applications, and in the spin-off of two companies, HORAMA and Advanced Biotherapeutics Consulting (ABC), dedicated to gene therapy of retinal diseases and preclinical research, respectively.

The positioning within Nantes University and Nantes University Hospital (“Centre Hospitalier Universitaire de Nantes”) and the support of these institutions in association to INSERM, is a major asset for the unit, bridging basic science to clinical research, in a multidisciplinary environment. The preservation of a good balance between basic and translational programs, and the sustainability of contacts for the young investigators, who are the leaders of the thematic groups, will be one of the challenges for the coming five years.

Strengths and opportunities in the context

- the unit shows a strong highly dynamic and well-structured organization;
- the unit has an international reputation in the field of rAAV based gene therapy;
- the unit benefits from an exceptional environment including academic local partners, unique facilities and core labs, clinical research units, reorganization and extension of university campus, dynamics of regional policies fostering translational research programs;
- the implication of young investigators is strong;
- the unit has a strong and focused scientific program.

Weaknesses and threats in the context

- the level of scientific publications does not fully reflect the dynamics and level of the scientific production;
- the long-term presence of key personnel, particularly thematic group leaders and experts of core facilities, is not secured;
- the number of international grants is insufficient (i.e. H2020);
- the move into the new IRS2 building of the University of Nantes might transiently spread the team, labs and instruments between two locations (IRS2 & IRS-UN).

Recommendations

- it is necessity to preserve a good balance between upstream and translational medicine research programs;
- the unit should accelerate the dissemination of results through peer reviewed scientific publications and establish a publication strategy to reach higher-level journals;
- the future management strategy will need to consider how to stabilize the position of thematic leaders;
- although the unit had an exceptional level of funding for its translational programs, applications to highly competitive grants and fellowships of National agencies (i.e. ANR) and of the European Commission (ERC, H2020 collaborative projects) may reinforce the visibility of its basic research programs and may improve the sustainability of funding in the future;
- the unit should increase the number of recruited postdoctoral scientists. This may need to enhance the visibility through adequate communication strategies;
- the immunology theme should be reinforced, through the recruitment of a young investigator with strong immunology background, and through a more integrated strategy with innovative vectorology to design rAAV vectors with increased tolerogenic capacity.