DPTM - Physiopathologie animale et biothérapies du muscle et du sytème nerveux

Rapport Hcéres

HCERES

High Council for the Evaluation of Research
and Higher Education

Research units

HCERES report on research unit:

Animal Pathophysiology and biotherapy for muscle and nervous system diseases

PAnTher

Under the supervision of the following institutions and research bodies:

ONIRIS - École Nationale Vétérinaire, Agroalimentaire et de l'Alimentation, Nantes-Atlantique

Institut National de la Recherche Agronomique - INRA

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]

Kevin TALBOT, 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:	Animal pathophysiology and biotherapy for muscle and nervous system diseases
Unit acronym:	PAnTher
Label requested:	UMR
Current number:	703
Name of Director (2015-2016):	Ms Marie-Anne COLLE
Name of Project Leader (2017-2021):	Ms Marie-Anne COLLE

Expert committee members

Chair:	Mr Kevin TALBOT, University of Oxford, Oxford, United Kingdom
Experts:	Mr François CASAS, Montpellier (representative of CSS INRA)
	Mr Laurent SCHAEFFER, ENS, Lyon
	Mr Rafael YÀNEZ, Royal Holloway, University of London, United Kingdom
Scientific delegate representing the HCERES:	Mr Jacques NOËL
Representatives of supervising institutions and bodies:	Ms Dominique BUZONI-GATEL, ONIRIS
	Mr Christian DUCROT, INRA
Head of Doctoral School:	Ms Corinne MIRAL, Doctoral School n° 502 “Biologie Santé”

1 • Introduction

History and geographical location of the unit

PAnTher is a small joint research unit, located at the Veterinary School of Nantes (ONIRIS), accredited by INRA division Animal Health (SA). In recent years the unit has evolved from a laboratory specialising primarily in veterinary pathology to a research driven enterprise, with a translational medicine focus in neuromuscular diseases. This includes a broader research collaboration in North-Western France in partnership with INSERM UMR 1089 (Nantes) and the Centre of Cell & Gene Therapy (Boisbonne Centre, ONIRIS) to form "Atlantic Gene Therapies" (AGT). To achieve this, the Unit has expanded its range of techniques, and has acquired the full range of functional tests for large animal work, biochemical and molecular techniques, including "omics" and high-resolution microscopy. It has also engaged with a number of important partnerships: EATRIS (European Advanced Translational Research Infrastructure in Medicine), BIOREGATE (Pays de Loire network for regenerative medicine), IBISA (Infrastructures en Biologie Santé et Agronomie), Biogenouest, ECTIS (European Centre for Transplantation and Immunotherapy Sciences - CESTI) and NeurATRIS (Translational research infrastructure for advanced therapies in Neuroscience).

The unit is organized around two activities: research on pathophysiology and translational therapeutics and the APEX platform, which provides a service in molecular pathology and animal phenotyping to the scientific community. Both groups share methodologies and core facilities, hold joint lab meetings and include veterinarians that are specialists in pathology and large animal models.

Management team

The INRA UMR 703 management committee consists of a head of unit (Ms Marie-Anne COLLE) and a deputy head of unit (Mr Karl ROUGER).

HCERES nomenclature

SVE1_LS4 Physiologie, physiopathologie, biologie systémique médicale

Scientific domains

Cell and gene therapy for Duchenne Muscular Dystrophy (DMD) and gene therapy of the nervous system.

Unit workforce

Unit workforce	Number on 30/06/2015	Number on 01/01/2017
N1: Permanent professors and similar positions	3	5
N2: Permanent researchers from Institutions and similar positions	1	1
N3: Other permanent staff (technicians and administrative personnel)	7	7
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)		
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	2	
N6: Other contractual staff (technicians and administrative personnel)	5	
N7: PhD students	4	
TOTAL N1 to N7	**22**	
Qualified research supervisors (HDR) or similar positions	3	

Unit record	From 01/01/2010 to 30/06/2015
PhD theses defended	3
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

PAnTher is a small joint INRA and ONIRIS research unit organized and run as a single research team. The PAnTher activities principally involve research, but also include important diagnostic, teaching and translational activities. PAnTher aims to develop therapeutic approaches for several hereditary diseases of muscle and central nervous system along two axes 1) Biotherapy, focusing on cell and gene therapy for DMD, Pompe disease and SMA; 2) Pathophysiology, with the aim to improving the understanding of the mechanistic basis of disease using animal models. The studies of the unit are based on integrated approaches from gene to animal such as functional tests, biochemical and molecular techniques. A major advantage is the variety of technical approaches afforded by the presence of the APEX (Anatomic Pathology Expertise for Research) platform, dedicated to pathology and phenotyping as a service.

PanTher works in a very competitive environment, namely the development of cellular and genetic therapies for inherited neuromuscular diseases, in which France is one of the international leaders. It benefits from a

comprehensive animal model approach encompassing rodents to Non-Human Primates (NHPs); this is a definite strength, sought by partners, and should be exploited for maximum benefit. In this context, (i) the demonstration of effective delivery of viral vectors through the CerebroSpinal Fluid (CSF) in NHPs and (ii) the correction of the Duchenne phenotype of the Golden retriever dog model by canine MuStem cells are significant preclinical achievements that showcase what PAnTher can offer in this field.

Global assessment of the unit

Given the size of the unit and the number of scientists, the level of scientific production is excellent with publications in very good scientific journals in the field. The development of the APEX platform is a major strength and plays a key role in the global research activity of the unit. The unit has demonstrated a significant level of success in obtaining funding, particularly at the national level. However, it is noted that PAnTher is not currently involved in European or other international projects. Non-permanent staff including students, post-doctoral scientists as well as technicians and engineers hired on fixed-term contracts are a critical part of the research team. There is a temporal trend towards an increase in the number of non-permanent staff that is evidence of the team's positive academic reputation and ability to attract high quality researchers. A key challenge for the unit is how to successfully manage the transition from a dedicated service unit to one engaged in primary research. The assessment panel recommend that the management team consider their internal research strategy in the context of other French groups working on similar projects, especially taking into account the overall AFM (Association Française contre les Myopathies) strategy for biotherapy of neuromuscular diseases. This will serve to help position their projects in the space where they are maximally competitive. In particular, translation of biotherapeutics into clinical trials is very challenging and requires considerable resources to overcome regulatory and logistical hurdles and cannot be achieved without the framework of bodies such as AFM. The panel further recommends the strengthening of the APEX platform and its involvement in animal diagnostic activities aligned with the core interests of ONIRIS and INRA.

Strengths and opportunities in the context

The unit clearly has an excellent reputation within its own institutional environment and is viewed as one of the leading laboratories in ONIRIS. The director has the strong support of the head of ONIRIS and this support is given both in recognition of the importance of APEX, but also because of the quality of the scientific research in the unit. This has been acknowledged by making the head of unit (Ms Marie-Anne COLLE) director of research for ONIRIS.

PAnTher is a resource of national significance, which is obviously highly valued by INRA because of the concentration of large animal expertise. This expertise underpins both the service provided by APEX and the training of veterinarians, which is a critical function of ONIRIS of economic importance to the nation.

The strength of PAnTher is the convergence of a significant number of well-trained technical/scientific personnel with a strong background in veterinary pathology, combined with molecular scientists focussed on human disease all working to develop therapeutic approaches using animal models. This creates an unusually high level of synergy.

The PAnTher unit is well integrated into several networks within France, chiefly Atlantic Gene Therapies, but also EATRIS, BIOREGATE, IBISA, Biogenouest, ECTIS and NeurATRIS. This mitigates its small size and allows its access to external expertise and collaborations.

The full ISO 9001 certification is a major asset, which is both a testament to the excellence of the unit but also facilitates the generation of income through external service work.

The APEX technical platform is another major strength of PAnTher. This platform is dedicated to the investigation of healthy and diseased animal tissues and represents an important concentration of diagnostic tools, which make the unit an attractive place for training.

The track record of PAnTher to raise national funds is excellent and the funding portfolio has diversified significantly in the last 5 years.

The unit culture is strong with good synergy between the different themes and between researchers and technicians. There is close hands on supervision by PIs. Modern omics and other technologies are available. All of this has improved in the last 5 years, during which time there has been an impressive consolidation of techniques and research activities.

The opportunity to build on existing PAnTher expertise for the exploration of novel therapeutic avenues and to expand the animal diagnostic activities of PanTher.

Weaknesses and threats in the context

PAnTher is a small unit. Despite its internal and external links, this makes it vulnerable, particularly when most of the work is in the ultra-competitive field of biological therapies.

There is a lack of space in which to expand the unit's research activities.

Although there are numerous external collaborative projects, PAnTher does not appear to have many highly developed internal collaborations within ONIRIS. The assessment panel formed the view that one contributing factor was the lack of a culture of collaboration in ONIRIS. The new head of ONIRIS clearly intends to prioritise the development of a more coherent research strategy, with PAnTher very much an integrated part. This should develop into an opportunity for PanTher.

Work on human diseases in PAnTher may be incongruent with the interests of the key stakeholders, INRA and ONIRIS, who by definition are constituted to improve and maintain animal, rather than human, health. This may be a factor that creates a barrier to the necessary expansion of personnel.

The impact factor of published papers resulting from work within the unit is currently in need of improvement. Selected outputs should be targeted to higher impact factor journals. The panel questioned whether the strategy for targeting research journals is correct.

The assessment panel was concerned that the investigators may underestimate the challenges in taking their discoveries as far as clinical trials. There is a lack of overall translational infrastructure at present and it would be important to strengthen clinical links that facilitate first-in-man studies.

The research in the unit is primarily technically led and focussed on solving problems of biological therapy delivery. This does not allow hypothesis driven research to produce genuinely novel insights into disease mechanisms. However, this is a minor criticism because a drive towards more mechanistic research would run the risk of reducing the focus on areas where the team is strongest.

The research programs are in highly competitive areas and are vulnerable to failure if other larger groups deliver effective therapeutic approaches that make those in this unit redundant (e.g., AAV-mediated therapies for SMA (Spinal Muscular Atrophy) developed elsewhere are close to the clinic at present). There is currently a lack of a clear mitigation strategy to deal with this possibility.

Recommendations

In recent years the unit has developed numerous and fruitful collaborations and obtained substantial grant funding. However, it is critical that the acquisition of future external funding is consistent with the strategy for internal research development within the unit.

There should be a consolidation of a critical mass of internal research in order to generate publications with increased impact factors and an increase in papers which are led from the unit, with one of the PIs as senior author, rather than contributions as middle author through collaborations.

The field of gene and molecular therapeutics is highly competitive. Therefore a concerted effort should be made to promote international collaboration. European networks funded by Horizon 2020 and E-Rare offer a good opportunity for bringing the unique skillset of PAnTher to a wider audience. An increase in visibility will help achieve stronger publications with higher impact and also promote collaboration.

The unit needs to expand the number of researchers in order to reduce its vulnerability. There is a lack of middle grade researchers (at post-doctoral level). This is a missed opportunity for the scientific community, given the outstanding training opportunities available at PAnTher. This could be approached by more aggressive exploration of other sources of funding, European and national. The legacy of being a service unit may be an inhibitory influence that must be overcome in seeking external project grant funding, which could facilitate the recruitment of more post-docs. Outstanding postdoctoral candidates may also be holders of personal fellowships.

The management team must work to limit any further divergence between their own research strategy and the agendas of ONIRIS and INRA. This requires open discussion and close liaison with the head of ONIRIS in particular.

APEX activity could be increased to generate income and strengthen their position within ONIRIS and INRA. They should consider expanding their service to more diagnostic work, which would generate income that could be used to fund research positions.