Translational gene therapy for retinal and neuromuscular diseases

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Translational gene therapy for retinal and neuromuscular diseases

From the

University of Nantes

INSERM

December 2010

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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: Translational gene therapy for retinal and neuromuscular diseases

Requested label: UMR_S INSERM

N° in the case of renewal: UMR_S 649

Name of the director: M. Philippe MOULLIER

Members of the review committee

Committee chairman:

M. Ali SAIB, CNAM, Paris

Experts:

M. Jacques IZOPET, CHU Purpan, Toulouse

M. François TROTTEIN, CNRS, Pasteur Institute, Lille

Mrs Mary COLLINS, University College London, London, UK

M. Moncef GUENOUNOU (CNU), Université de Reims

M. François LEMOINE (CSS INSERM), Université Pierre & Marie Curie, Paris

Observers

AERES scientific advisor:

M. Yves GAUDIN

University, School and Research Organization representatives:

M. Jacques GIRARDEAU, University of Nantes

Mrs Catherine LABBÉ-JULLIE, INSERM

Report

1 • Introduction

- **Date and execution of the visit :**

The visit was performed the 13th of December 2010 from 13h15 to 18h30. After the introduction talk from the head of the laboratory, the main PIs were invited to present their work and project. This was followed by a general discussion focusing on science first, then on governance and general strategy. The committee then met successively in the absence of the director, students and post-docs, technicians and engineers, researchers and teachers/researchers. The visit ended by a closed-door debriefing of the committee.

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

Since 1996, the research used recombinant viral vectors including rAAV vectors to develop gene therapy strategies for inherited diseases. During the last years, UMR INSERM 649 focused on rAAV related technology and development of pre clinical models in order to validate geen therapy strategies. A preclinical vector core as well as a large animal core has been built and developed with an IBISA labelling. Using these platforms, validations of different gene therapy strategies have been validated using preclinical large animal models leading to the implementation of clinical trials. In addition, the research unit has proposed to study the mode of delivery of rAAV vectors, the molecular characterization of recombinant DNA, epigenetic status of the vectors within the tissue and the relationship between the host immune system and the vectors.

- **Management team :**

The head of the unit, Philippe MOULLIER, is a DR2 INSERM. The research unit is organized and run as one single research team with two PIs (both DR2 INSERM). Both PIs participate to the management of the unit.

- **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)	2	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	3
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	6	5
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	1	1
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	6	7
N6: Number of Ph.D. students (Form 2.7 of the application file)	4	5
N7: Number of staff members with a HDR or a similar grade	5	5

2 • Overall appreciation on the research unit

- **Summary :**

In the last years, beside the research activities, different platforms for preclinical vector core, large animal core and GMP grade vector core has been built and labelled as IBISA platforms. Using these tools, the research is mainly focused on the use of rAAV vectors to develop gene therapy strategies for neuromuscular and retinal inherited diseases. Objectives are to validate strategies using large animal preclinical models (cats, dogs, monkeys); to evaluate the immunological aspect of the use of rAAV vectors (immunotoxicity, immune response and control of immune by inducing tolerance against vector and transgenes), to test different modes of delivery of rAAV vectors and to study epigenetic status of vectors once delivered within the tissue.

- **Strengths and opportunities:**

- Strong and visible expertise in the field of AAV based gene therapy.

- Unique access to large animal models.

- Very good clinical pipelines from pre-GMP production to phase I trials.

- Dynamic organization of the lab including fundraising.

- **Weaknesses and threats:**

- Lack of support from the university.

- Too many people in non academic position with low turn over.

- Concerns about the relevance of some animal models for preclinical studies.

- **Recommendations:**

- The Unit has to attract foreign post-docs and students.

- The goals of the immunological program should be clarified.

- There is a need to implement clinical trials within the next assessment period.

- There is also a need a global strategy from the institutions and the lab to coordinate and build a larger gene therapy effort in Nantes.

- **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	4
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	5
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	
A4: Number of HDR granted during the past 4 years	0
A5: Number of PhD granted during the past 4 years	6

3 • Specific comments

- **Appreciation on the results:**

In the last years, the head of the unit has contributed strongly to the development of a preclinical vector core a BL2/BL3 large animal core in collaboration with the veterinary school and more recently to a GMP grade vector core in collaboration with EFS. All these platforms received an IBISA labelling and represent an important and relevant support for the development of the research. However, they are not part of the present evaluation.

The research activities are based on the development of gene therapy strategies for inherited diseases using rAAV vectors. Due to the expertise and the know how in the field of rAAV vectors and in the use of preclinical large animal models, the research is original and is focused on translation to the clinic.

The two leaders of this research unit work on the development of rAAV gene therapy for neuromuscular inherited diseases and retinal inherited with clinicians and other national partners in this field (AFM, Institut of Myology) respectively. The researchers have established strong partnership with EFS and veterinary school. They participate at european and international levels to different networks (Clinigene Network of Excellence) and have strong collaborations with the University of Florida.

The research team is publishing regularly in the top journals of the speciality such as Molecular Therapy (n= 10, IF= 6.8) and Journal of Virology (n= 3, IF = 5.5). 26 publications have been published since 2006, whose only 5 of them are from collaborations.

However the number of graduate PhDs is relatively low and the quality and a small number of publications could be published in higher impact journals.

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

Both leaders are invited to national and international meetings at least once a year. Students also participate in national meetings and even in some cases in international meetings (ASGT and ESGT). The laboratory is capable of recruiting master and PhD students locally or at the national level. In 2010, a post-doc has been recruted for a CR1 INSERM position.

However attracting students or post-docs from abroad has not been successful. This may be reinforced in the future by a tight collaboration with the University of Florida with possibilities of international exchanges.

Leaders are able to raise funds either from local donations and private enterprises or from AFM. The strong support of AFM allows to maintain the salaries of numerous students, post-docs, technicians and engineers.

However, the support from the university appears very low, except concerning housing in the university building.

- **Appreciation on the management and life of the research unit:**

The research unit organisation is well structured with two small groups in a whole unit each directed by a leader. Lab meetings and invited conferences are regularly organized. Students and techincians can participate in teaching activities as well as technical formations. They can also participate in scientific presentations at meetings.

- **Appreciation on the scientific strategy and the project:**

The project of the reseach unit is to develop translationnal research for gene therapy of inherited diseases based on the use of rAAV vectors from bench to bedside . This project is a continuum of the previous research with the goal of enhancing translationnal gene therapy activities for retinal and neuromuscular inherited diseases.

Both projects rely on development of animal models with their avantages and their limits.

Concerning retinal inherited diseases, three projects are mainly in development, and one is almost ready to start for a clinical trials (RPE 65 gene therapy). Recent data on a phosphodiesterase 6 beta deficiency are promising for future clinical developments.

Concerning neuromuscular inherited diseases, projects for Duchenne disease as well as spinal muscular atrophy are part of collaborative networks with AFM, Genethon and Institute of Myology (Pitié Salpêtrière). The later project concerning SMA has been recently reinforced by the arrival in the research unit of a neurosurgeon whose the goal is to test different strategies for injecting rAAV vectors in the CNS. These projects are very ambitious and are long term project. With the strong support from AFM and the expertise and know how of the searchers in the field they appear feasible.

Different important questions regarding vector integration, epigenetic modifications as well as immune response and immune tolerance are addressed. However, the immune project should be clarified particularly concerning the development of strategies based on the induction of tolerance. Stronger collaborations with other immunologists in Nantes will be helpful.

Finally, to avoid exclusive private-derived fundings, a support from the academic institutions such as the university is needed.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
TRANSLATIONAL GENE THERAPY FOR RETINAL AND NEUROMUSCULAR DISEASES	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**

UNIVERSITÉ DE NANTES

PRÉSIDENCE DE L'UNIVERSITÉ
DIVISION DE LA RECHERCHE
ET DES ÉTUDES DOCTORALES

Nantes, le lundi 7 mars 2011

REF : JG/PTi - 2011 RECH N°258
SUIVI PAR : Jacques GIRARDEAU
Objet : Rapport d'évaluation - S2UR120001436 - Translational gene therapy for retinal and neuromuscular diseases - 0440984F

LE PRÉSIDENT

à

Monsieur Pierre GLORIEUX
Directeur de la section des unités de recherche
AERES

Monsieur le directeur,

Je vous fais parvenir ci-dessous les commentaires de portée générale sur le rapport d'évaluation de notre unité « Translational gene therapy for retinal and neuromuscular diseases », dirigée par M. Moullier :

- Partie 2 *Overall appreciation on the research unit*, paragraphe *Strengths and opportunities* (p.4), la phrase commentée : "**The goals of the immunological program should be clarified**"

The immune program includes different projects that are complementary as they share the common goal to induce tolerance towards the transgene after rAAV delivery in the muscle, using generally the same gene transfer model in the primate. During the oral presentation and because of limited time, we unfortunately didn't have the opportunity to present all these projects to show complementarity. We believe that it is important to combine the overall knowledge acquired from these strategies to achieve the goal of the program.

- Partie 5 *Specific comments*, paragraphe *Appreciation on the scientific strategy and the project*, (p.6), la phrase commentée : "**Stronger collaborations with other immunologists in Nantes will be helpful**"

- We don't see how our long last collaboration with immunologists in Nantes could be thighter ?
- We share grant applications and financial resources and regular joint meetings.

Je vous prie d'agréer, Monsieur le directeur, l'expression de mes sentiments les plus cordiaux.

Yves LECOINTE

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