Centre de recherche en Myologie

Rapport Hcéres

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

Department for the evaluation of research units

AERES report on unit:

Research Center for Myology

Under the supervision of the following institutions and research bodies:

Centre National de la Recherche Scientifique

Institut National de la Santé Et de la Recherche Médicale

Université Paris 6 - Pierre et Marie Curie

February 2013

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

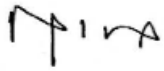
Research Units Department

President of AERES

Didier Houssin

Research Units Department

Department Head



Pierre Glaudes

The president of AERES "signs[...], the evaluation reports, [...]countersigned for each evaluation department by the relevant head of department (Article 9, paragraph 3, of french decree n°2006-1334 dated 3 november 2006, revised).

Grading

Once the visits for the 2012-2013 evaluation campaign had been completed, the chairpersons of the expert committees, who met per disciplinary group, proceeded to attribute a score to the research units in their group (and, when necessary, for these units' in-house teams).
This score (A+, A, B, C) concerned each of the six criteria defined by the AERES.
NN (not-scored) attached to a criteria indicate that this one was not applicable to the particular case of this research unit or this team.

Criterion 1 - C1 : Scientific outputs and quality ;
Criterion 2 - C2 : Academic reputation and appeal ;
Criterion 3 - C3 : Interactions with the social, economic and cultural environment ;
Criterion 4 - C4 : Organisation and life of the institution (or of the team) ;
Criterion 5 - C5 : Involvement in training through research ;
Criterion 6 - C6 : Strategy and five-year plan.

With respect to this score, the research unit concerned by this report and its in-house teams received the following grades:

- Grading table of the unit: Research Center For Myology

C1	C2	C3	C4	C5	C6
A+	A+	A+	A	A	A

- Grading table of the team 1: Genetics, Pathophysiology & Therapeutic approaches of muscle diseases

C1	C2	C3	C4	C5	C6
A+	A+	A+	A+	A	A+

- Grading table of the team 2: Pathophysiology and Therapy of Dynamin 2-related centronuclear myopathy

C1	C2	C3	C4	C5	C6
A+	A	A+	NN	NN	A

- Grading table of the team 3: Regeneration, Pathophysiology & Therapeutic Approaches: Cellular Models

C1	C2	C3	C4	C5	C6
A+	A+	A+	A+	A+	A+

- Grading table of the team 4: Pathophysiology & Biotherapy of Myotonic Dystrophy

C1	C2	C3	C4	C5	C6
A+	A+	A+	NN	NN	A+

- Grading table of the team 5: RNA-Repair based Therapeutics & Skeletal Muscle Pathophysiology

C1	C2	C3	C4	C5	C6
A+	A+	A+	A	A	A

- Grading table of the team 6: CNS Gene Transfer & Biotherapy of Motor Neuron Diseases

C1	C2	C3	C4	C5	C6
A	A+	A+	B	B	A

- Grading table of the team 7: Myasthenia Gravis: Etiology, Physiopathology & Therapeutical Approache

C1	C2	C3	C4	C5	C6
A	A+	A+	A	A	A

- Grading table of the team 8: Development & Stem Cells

C1	C2	C3	C4	C5	C6
A+	A+	A+	A	A	A

- Grading table of the team 9: Cytoskeleton Architecture & Cell Polarization

C1	C2	C3	C4	C5	C6
A+	A+	A+	A+	A	A+

- Grading table of the team 10: Inflammatory muscle and targeted innovative therapy

C1	C2	C3	C4	C5	C6
NN	NN	A+	NN	NN	A

Evaluation report

Unit name:	Research Center For Myology
Unit acronym:	
Label requested:	UMR,
Present no.:	UMR974, UM76
Name of Director (2012-2013):	Mr Thomas VOIT
Name of Project Leader (2014-2018):	Mr Thomas VOIT

Expert committee members

Chair:	Ms Anne FERNANDEZ, CNRS, IGH, Montpellier
Experts:	Ms Joëlle AMEDEE-VILAMITJANA, Université Bordeaux Segalen (representative INSERM)
	Ms Nathalie CARTIER-LACAVE, CEA/INSERM, Paris
	Ms Mireille CLAUSTRES, Montpellier University (representative of the CNU)
	Mr Mauro GIACCA, International Centre for Genetic Engineering and Biotechnology, Trieste Italy
	Mr Pierre GILLET, CNRS Nancy (representative of the CNRS)
	Ms Nathalie GOEMANS, Kliniekhoofd Kinderneurologie-NMRC Kinderen, Leiden, Belgium
	Mr Johnny HUARD, Stem Cell Research Center,Pittsburgh, USA
	Mr Christopher E. PEARSON, The Hospital for Sick Children, Toronto, Canada
	Mr Laurent SCHAEFFER, ENS Lyon
	Ms Naomi TAYLOR, CNRS, IGMM, Montpellier
	Mr Laurent TIRET, Ecole nationale vétérinaire de Maisons-Alfort

Scientific delegate representing the AERES:

Mr Bernard DASTUGUE

Representative(s) of the unit's supervising institutions and bodies:

Mr Thierry GRANGE, CNRS

Mr Paul INDELICATO, UPMC

Ms Catherine LABBE-JULLIE, INSERM

Mr Stéphane ROQUES, General secretary, Institute of Myology

1 • Introduction

History and geographical location of the unit

The Research Centre for Myology is set in the particular environment of the Institute of Myology (IM), based on a public-private partnership between the Association Française contre les Myopathies (AFM), represented by the Association Institut de Myologie (AIM – both charitable societies) and by public institutions, UPMC, INSERM, CNRS and AP-HP (Hospital facilities).

The IM was founded in 1996 on the site of the university hospital "Pitié-Salpêtrière", with the goal of providing an integrated interdisciplinary centre gathering expertise ranging from research in fundamental myology and neuromuscular disorders to the care of patients with the additional goal of developing innovative therapeutic approaches. This privileged structure of the IM houses the largest French Reference Centre for Neuromuscular Disorders, an NMR research department, an integrated platform for functional evaluation and a Clinical Trials Unit as well as a human cultured muscle cell resource, the biobank MYOBANK, associated to the EUROBIOBANK resource.

Management team:

Mr Thomas VOIT, Director of the unit.

Unit workforce

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	8 [3,2]	11 [4,4]	7
N2: Permanent researchers from Institutions and similar positions	28 [24,4]	35 [28,4]	22
N3: Other permanent staff (without research duties)	18 [18]	21 [21]	14
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)			
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	23 [23]	23 [21,35]	14
N6: Other contractual staff (without research duties)	14 [13,5]	14 [13	4
TOTAL N1 to N6	**91 [82,1]**	**104 [88,15]**	**61**

Percentage of producers	***100 %***

Unit workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	15	
Theses defended	13	
Postdoctoral students having spent at least 12 months in the unit*	31	
Number of Research Supervisor Qualifications (HDR) taken	6	
Qualified research supervisors (with an HDR) or similar positions	22	27

2 • Assessment of the unit

Strengths and opportunities

The strength of the Myology Research Center stems from its original goal and historical "raison d'être": To develop fundamental myology knowledge and translate this knowledge into clinical applications and therapies for muscle diseases. This objective is pursued with the incitus and continued interaction with the medical university environment and support from the AFM and AIM, and an accounting of this progress is shared with the general public.

The center now represents a unique cluster of both excellent basic research on skeletal muscle and clinical research on therapeutic applications. The translational aspect of the current mix of research programs is exquisite on a global international scale.

This important translational goal, promoted on a theoretical basis for all biomedical research, is here at work and creates a highly motivated and cohesive spirit throughout all categories of personnel involved, from technicians to group leaders.

Weaknesses and threats

Space re-unification is a critical issue for the future unit. Teams have been and still are geographically separated from each other at opposite sides of the hospital campus. This has been hampering the teams from functioning in an integrated manner – which is one of the strengths of the collection of complementary specialists present in the project. Furthermore, this geographical separation imposes the duplication of both space and costs for access to communal facilities and equipement. Not only is the current investment in the established momentum of translational research at risk, but the continued participation of key members, as well as the possibility to attract new important teams, are severely hampered by this situation– as many of the researchers are of the caliber that they will be cherry-picked by other research institutes in various countries.

The other potential weakness of the unit stems from its strength: the essential contribution and support from the AFM, a charitable society, is dependent on the yearly success of its telethon. In addition, the teams have an intrisinc handicap in obtaining funding from other institutions and societies, as they are 'tagged' as being well supported by the AFM/AIM; and although the unit plans on gaining more funding autonomy through exploitation of IP rights, this is still very minor and will require long-term investments before a significant return from IP rights can be anticipated.

Another concern is with respect to the strategic choices made by the AFM; the possibly excessive prioritization of clinical trials can result in a detrimental shift away from basic research promoting fundamental mechanistic understanding of muscle biology and diseases.

Recommendations

It is crucial for all researchers to be housed within the same research building, thus sparing both common lab space and money for equipment investment and maintenance and keeping an attractive momentum for new groups to join in the unit. This issue, already raised by the previous AERES committee, is a concern DEMANDING PRIORITY. The translational research from the current mix of research programs can only fully realize its interactive potential when the teams will be geographically unified in their work-space. This point will hopefully be resolved through the already ongoing discussions between the funding institutions and the UPMC to identify a dedicated space for the Centre.

Function and execution of the Transversal Axes will rely on the implementation of a clearly defined mandate given to the young scientists responsible for each of the axes, as well as their awareness of the ongoing projects in the whole of the Centre. The success of the cohesion of the Centre will depend upon the success of the continued cohesiveness and the evolution of those interactions between all the Teams.

Provision for extending and strengthening the unit's interactions and privileged communications between researchers working in the two neighbouring research centers on site (the Cardiology Center and the Neurology Institute, ICM) would be a real plus.

For the complementary efficiency of the transversal axes to be effective, it is also essential that a fair financial and technical support be assured to teams implicated in high quality research in fundamental myology as well as those implicated in the translational application of this research into therapeutical avenues.

3 • Detailed assessments

The site of the Hospital "Pitié-Salpêtrière" hosts two research units specialized in the field myology and muscle physiopathology, as part of the "Institut de Myologie" (IM):

- INSERM U787, "Myology group" is located at the 105 bvd de l'Hopital

- UPMC UM 76, INSERM U 974, CNRS UMR 7215 "Therapy of striated muscle disorders", where the visit took place, is located in the Babinsky building, 800 meters away from Unit 787, on the other side of the hospital campus.

Since research efforts concerning Myology are dispersed between these two geographically separated research Units, as critically raised by both the previous AERES committee and the international SAB of the Institute of Myology, the strategy proposed for the new unit is to gather these forces within a unique "Research Centre for Myology", spanning from fundamental cell and developmental biology through pathophysiology, muscle-related immunology and innovative models to develop translational research in pre-clinical and clinical trials for rare muscle diseases.

Assessment of scientific quality and outputs

This combination of expertise and the biomedical environment of the Hôpital Pitié-Salpétrière makes the Research Centre for Myology, through the integration of the various aspects of myology, unique in Europe. This represents a truly effective translational research unit not only from basic sciences to clinical applications, but also in an essential feed-back, from clinical studies back to fundamental knowledge and understanding of the molecular basis of Neuromuscular Diseases.

The themes covered by the 10 research teams span the different fields of myology from fundamental research in cell biology through pathophysiological research for selected model diseases to translational medicine with innovative pharmacological, cell-, pharmaco-gene and gene therapy approaches at the pre-clinical and clinical levels.

While fundamental research into the developmental and pathophysiological concepts are considered the essential basis for understanding the pathophysiology of disease and constructing rational therapy, the reverse dynamics, taking advantage that clinical research can feed-back onto basic research, provide powerful new avenues for discovery. This dual strategy positively impacts on both fundamental and translational aspects of research, focusing on rare neuromuscular diseases as benchmarks towards more general topics of public health.

The scientific output of the unit in terms of publications is quantitatively and qualitatively very good with over 400 articles in peer-reviewed journals in the 5 years spanning from 2007 to 2012, including top-level publications in journals such as NEJM, JAMA, Nature, Cell, Dev Cell, Nat Genetics, Nat Med and Nat Struct Mol Biol. Importantly the bibliometric analysis of the visibility for this output through citations of the published work, shows that 1/4 of these publications are in the top 10% most cited, with 30% of them with major authorships from groups in the unit.

The unit has been successfully granted 17 patents, of which many are at the border of fundamental science and its translational application, documenting a high innovative potential. Of importance, several of these patents have given rise to programs currently going towards clinical application (U7 technology for Duchenne Muscular Dystrophy (DMD), AAV9 systemic and intra- cerebro-ventricular targeting of α-Motoneurons for spinal muscular atrophy (SMA)), and others are being licensed by third parties or resulting in the formation of new biotech companies (e.g. Moviplate by GSK, PROSENSA, SAREPTA).

Assessment of the unit's academic reputation and appeal

The Centre has established reciprocal clinical and research links with other neuromuscular research groups throughout Europe and has developed cross-cutting collaborations. Important strategic partnerships have been developed into structured contracts with international centres: the LIA supported by INSERM and UPMC with the Fiocruz Centre at Rio de Janeiro, Brazil; the Collaboration Agreement between UPMC, AIM and the National Institute of Neuroscience, Tokyo, Japan; and the International Postgraduate School for Myology MYOGRAD jointly created between UPMC and the Freie Universitat in Berlin.

Teams are currently involved in 4 EU-funded networks (ENDOSTEM, FIGHT-MG, MYOAGE, SKIP-NMD) and are coordinating 2 of these networks (FIGHT-MG and MYOAGE).

The unit is actively attracting and teaching international high calibre students, through the international postgraduate school, MYOGRAD (40 students over 5 years) as well as through structured international collaborations (Brazil, Japan, EU networks).

The IM is a founding member of the recent AFM-created network BIRD (Biotherapy Institutes for Rare Diseases) together with the Genethon and iStem (both situated in Evry) and the Atlantic Institute for Gene Therapy (Nantes). This network is viewed as essential to the research context by creating synergies within large multidisciplinary working groups centered on immune therapy- or gene therapy approaches for muscular dystrophy or spinal muscular atrophy including vector production under GMP conditions (Genethon) and large animal facilities (AGTI, Boisbonne, Nantes), or creation of models for high throughput screening (iStem).

Assessment of the unit's interaction with the social, economic and cultural environment

As per their intrinsic implication and mission with the AFM, all teams sustain a continued promotion, social dissemination and public visibility of their research activities through direct communication with patients' families such as at the “Journées des Familles” attracting 1500-3000 patients and families or the "Université AFM des maladies rares", and the yearly Telethon, organized by the AFM.

Dissemination of the unit’s prominent findings and important advances in the field is also assured through regular reports such as a bimonthly Newsletter of the Institute (bilingual English/French) sent out to over 1000 readers worldwide with interviews, and reviews of interesting developments in a lay-adapted manner. Results are also communicated to the community of French neuromuscular patients through the AFM newsletter VLM.

In addition, several unit members play an active socio-scientific role in translating research in France and abroad, such as via a mandate by the Ministry of Research to lead a commission on research into ageing or participation as an expert member in the French anti-doping agency. The unit Director also holds roles as a president or member for different commissions of the German Ministry of Research for the German excellence initiative.

Importantly, some of the tools and findings developed in the unit also find obvious application to more general critical medical issues such as muscle ageing and the quantitative evaluation of sarcopenia.

The unit has made very significant advances towards pre-clinical and clinical trials using specifically developed AAV vectors. First, they are advancing towards double exon skipping U7 correction of DMD (and switching from AAV1 to AAV8 because of an improved biodistribution into heart and skeletal muscle); the therapeutic doses and preclinical data from GRMD injected dogs were analyzed in collaboration with Genethon and the Atlantic Institute for Gene Therapy (AIGT) Nantes, thus enabling them to obtain a meeting with AFSSAPS, to move onto formal toxicology studies with the goal of performing phase 1-2 trials of loco-regional AAV8-U7 exon skipping in 2014.

Secondly, they have made headway towards the treatment of motoneuron diseases and other CNS disorders; one group made the early breakthrough finding that scAAV 9 vectors are capable of transducing, after systemic application, CNS cells including α-motoneurons in the spinal cord thus crossing the blood brain barrier. In a highly competitive international context, the group has been very active in securing the IP for this finding with 2 patents in 2007 before its publication in 2009 and has recently shown, using scAAV9-SMN1 delivery in an early lethal delta7 smn mouse model, that the spinal muscular atrophy (SMA) phenotype can be rescued with the additive effect of substantially reversing SMA pathology when using concurrent intra-cerebro-ventricular and intravenous delivery of scAAV9. The approach is currently being developed into a pre-clinical project in collaboration with Genethon.

With respect to advances for cell therapy of NMD, another team in the unit is involved, in collaboration with the ENT (ORL, in French) department of the Tenon Hospital at UPMC, in an initial trial using autologous cell therapy for OPMD (OculoPharyngeal Muscular Dystrophy) based on the observation that the cricopharyngeal muscle of these patients shows precocious ageing as compared to the quadriceps muscle. The outcome of this first clinical trial has already shown encouraging results and a second phase of public funding to extend a phase 2 trial has been secured.

Along this line, the unit is currently negotiating strategic partnerships with a number of industrial third parties (SHIRE for the exploitation and development of VLA4; ProQR Therapeutics B.V. for AAV and trans-splicing technology; SANOFI, GSK, and JAIN Foundation for immortalized myoblasts for drug screening).

Assessment of the unit's organisation and life

The proposed Myology Research Centre will comprise 10 different teams actually integrated as parts of 3 different research units. Teams 1-7 were previously part of the unit "Therapy of striated muscle disorders". Teams 8 and 9, were both founded as AVENIR teams (designed to promote the independent careers of starting scientists) during the previous funding period and were part of the "Myology group", the other myology research unit (housed at 105 Bd de l'Hôpital). Team 10 is a new emerging research team that was previously affiliated with UPMC/CNRS UMR7211, INSERM U959. Together, the 10 teams represent a working force of more than 100 researchers, engineers, post-docs and Ph.D. students.

Importantly, to achieve the prioritized translational goal of the unit, the clinical Service of Internal Medicine which is tightly affiliated to the IM, houses a gene therapy unit and is authorized for phase 1-3 clinical trials (agreement n°10161M).

Together with the Director, direction is assured by a Steering Committee, which comes together at least once a month and decides on questions of scientific strategy, budget, and personnel. It reports to the Laboratory Council, which holds at least 4 meetings/year. The Centre is also evaluated and advised by an International Scientific Advisory Board, which meets in the center once a year but can also intervene, in addition, by electronic communication. The objective and strategy of the project are based on reciprocal and constant exchanges between bench and bedside, applied both for fundamental research and therapeutic application in absolute coherence with the setting and environment of the unit and the array of teams involved. This crosstalk strategy enables the unit to focus on rare neuromuscular diseases as benchmarks towards more general concerns of public health whenever applicable.

Pooled resources are available in terms of 1) Histopathological and NMR facilities with experts in human muscle morphology and neuromuscular diseases (NMD); and 2) A human primary cell culture and cell immortalization facility developing myoblast line models for specific NMD.

The technical and engineer staffs members report no conflict, with appropriate communication and access to training courses for carrier evolution. They also see that their situation will improve when the two sites of the unit will be geographically united.

One concern pointed out throughout the visit of the committee is the physical separation between the two parts of the Centre (the Babinsky and 105 bd de l'Hopital buildings) preventing easy and regular interactions between complementary teams, even if they have organized a face-to-face meeting every two months. The 15 min walk between the two buildings appears as a true barrier, and students and post-docs think this situation is detrimental for their research, and hinders the evolution of synergistic interactions that should clearly be active. Thus, there would be a major benefit if the two units were merged into a unique building.

The communication between students and their group leaders as well as with the Director seems very fluent and no conflict has been reported. A clear procedure for recruitment of young scientists for a permanent "CDI" position after their post-doc contracts expire is recommended: some positions have been filled without internal or external advertising. More transparency concerning the selection criteria is needed.

The Centre presents very good scientific leadership parity, with 4 out of 10 Teams leaded by female scientists and the associate director is female.

Assessment of the unit's involvement in training through research

Members of the unit have developed activities to foster and strengthen education in Myology at different levels: staff members are teaching at the Master1 and Master2 levels; team leaders are co-organizing two Master2 Programs "Biology of Ageing" and "International Stem Cells", and a PhD program entitled “Complexity of life” with UPMC.

An International M2 Program (Biotherapies and Immunology) is currently being put together between UPMC and Fiocruz. An International Postgraduate Program, MYOGRAD, was set up between UPMC and Berlin enabling 40 PhD projects to be funded over 5 years (2010-2014). Several members participate in the Inter-University Diploma of Myology teaching (Paris-Marseille) every year.

Most PhD students in the unit benefit from French national fellowship grants (MRT) and all of them belong to the same Doctoral School within UPMC (ED515 Complexité du vivant, University Pierre et Marie Curie, subtitled Sorbonne universities, www.ed515.upmc.fr), with a partnership with the first European post-graduated School for myology (MYOGRAD).

Of note, the Committee has been surprised that none of the students has been supported by a CIFRE grant. The numerous collaborations and grants that have been established, or are in the process of being set up, by the Centre with big Pharma and SMEs may promote this attractive and efficient funding mechanism in the future.

There is a well planned organisation to favour scientific exchange with internal seminars and work-in-progress meetings where students and post docs present their ongoing projects, Journal Clubs dedicated to students and post docs (including English spoken team meetings for some groups), national and international invited lectures. It is though recommended that all students be encouraged to present their work in English via seminar series in the institute at least once a year. Both doctoral students and post-docs seemed very satisfied with their management. They expressed their feeling that there was fair authorship distributions in articles, presentations or communications, and that they regularly participated as authors to national and international congresses or meetings. The PhD students did not feel it necessary to add any other committee (such as a "tutorat") as they already have a yearly evaluation meeting with their thesis committee ("comité de thèses") organized through the Doctoral School.

Overall, the PhD students and post-doctoral fellows expressed their enthusiasm for the type and level of research that is performed within the Myology Institute (including contact with clinicians and patients) and felt very supported by their advisors and group leaders. The vast majority consider working at the Center positively in terms of career development, and would recommend this Centre to other students and post-docs.

However, both students and post-docs, who are major workforce contributors and key transmitters in future training, unanimously expressed one concern: the consequences of the "Loi Sauvadet" on the capacity of non-permanant staff to continue carrying out their immediate scientific project and their future carriers. For all the 35 young scientists present at the meeting the unforeseen and brutal consequences of this law, precipitating the ending of their employement contract before the completion of their scientific project, dramatically compromises their opportunities to succeed in an academic career in France. This situation is seen as a programmed catastrophe for a whole generation of future researchers in France.

Of note the problem impacts less severely on the technical and engineer staff of this Research Centre because of the possibility of obtaining private financing through the AIM.

Assessment of the five-year plan and strategy

The 10 teams composing the Myology Research Centre cover several complementary aspects that fit perfectly within the general goal of the unit and provide synergy to the whole project by focusing on i) a better knowledge and understanding of the mechanistic bases of both major and rare neuromuscular diseases, ii) a continued advance on basic research on normal and pathological muscle development with expertise and access to important animal and cell models as well as knowledge databases and iii) strong partnerships with key public and private actors for true implementation towards translation in applied therapeutic strategies in pre-clinical and clinical trials.

Each of the 10 teams has outlined its specific research objectives which span across a track from fundamental to applied research and different themes are logically spread between these fundamental and applied sides of their research without absolute separation. Transversal to this is the concept of investigating individual disease mechanisms or models ranging in their reach from one end to the other, with the transversal dimension that different themes from muscle homeostasis to regeneration or aging and immunology can be more heavily oriented towards either the fundamental aspects and basic research, or towards their translational application.

In that respect, the project is certainly one of the strongest examples of an effective association of basic and applied research. The future unit has already secured the key academic and private partnerships and networks for both funding and clinical implementation of their research. The unit has made a good analysis of its strengths and weaknesses and provided with a unified geographical space for the 10 teams and a continued support from their key sponsor, AFM-AIM, promoting a balanced quality of their fundamental basic research, the five year proposed plan has an excellent feasibility.

4 • Team-by-team analysis

Team 1 : Genetics, Pathophysiology & Therapeutic approaches of muscle diseases

Name of team leader: Ms Gisèle BONNE

Workforce: 21-23 people

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	3 [1.6]	2 [0.6]	2
N2: Permanent researchers from Institutions and similar positions	10 [6.4]	10 [6.4]	6
N3: Other permanent staff (without research duties)	5 [5]	6 [6]	4
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)			
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	4 [4]	2	2
N6: Other contractual staff (without research duties)	3 [3]	1 [1]	1
TOTAL N1 to N6	**25**	**20**	**13**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	3 =>2	
Theses defended	3	
Postdoctoral students having spent at least 12 months in the unit	5	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	5	4

• Detailed assessments

Assessment of scientific quality and outputs

This team is fully dedicated to three groups of NMDs including retractile myopathies and cardiomyopathies, using the most appropriate tools to define the molecular causes and understand the pathophysiological bases of these disorders, and then to conceive and develop new therapeutic avenues. Research is carried out on biological material from patients as well as on various animal models that they have developed for each of the NMDS of interest. The team comprises approximately 30 persons, with three senior researchers in charge of their own projects (1 DR2 and 2 CR1 INSERM), 8 permanent research assistants and 6 associated clinical experts (1 PUPH and 5 PH). At the time of the visit by the committee, the non-permanent staff included 2 post-docs, 2 research assistants, 2 PhD students and 2 Master students.

Over the last four years, the team has been very active in defining the genetic and clinical spectrum and the natural history of Emery-Dreifuss muscular dystrophies and other laminopathies, collagen type VI-related muscle disorders, as well as dynamin 2 related centronuclear myopathies. Several genes and/or modifiers have been identified and pertinent animal models including knock-in humanized mice models and morphants zebrafish lines have been produced to investigate the physiopathology of muscle function/dysfunction and test new therapies.

Scientific productivity has been quantitatively and qualitatively very good, in particular as a result of fruitful international collaborations establishing genotype-phenotype correlations in NMDs. Twenty five articles (15% of the team production) have been published in the top 10 journals in the field including Nat. Medicine, Science or Dev. Cell., of which 10 publications from members from the team as first and/or last authors, The overall production of the team thus reflects its strong anchorage in international networks as well as the ability to foster original projects in disease mechanisms and preclinical trials. As an integral part of the team's objectives, they aim to develop a wide spectrum of genotype-phenotype correlations. To this end, the team has established dedicated locus-specific genetic and clinical databases with international contribution and visibility.

Assessment of the team's academic reputation and appeal

The team is locally, nationally and internationally well-inserted in a medical genetics continuum, associating clinicians, pathologists, molecular biologists, geneticists and diagnostic laboratories, that give access to large cohorts of patients facilitating the transfer from research to diagnostic applications (the team leader benefits from an interface contract with the hospital). The team has structured biobanked materials and cell lines, and participates as coordinator or partner in national and international funded networks and as curators for dedicated disease-orientated databases, thereby illustrating the attractivity of their work and their successful translational research. All these efforts have resulted in a major contribution to our understanding of the pathophysiological mechanisms of NMDs of interest.

The team is a world leader in laminopathies, being among the 5 top groups in the world in LMNA mutations and members are actively involved in the organization or co-organization of international workshops and congresses. They have also established long-standing collaborations with several international universities.

Assessment of the team's interaction with the social, economic and cultural environment

The team is very well funded (EU, ANR, AFM, INSERM, foundations…)

It is very active in the social dissemination of research activities through direct interaction with patients' families such as at the “Journées des Familles” or the "Université AFM maladies rares", organized by the AFM. Several researchers have also participated in a program for Young students at secondary school level. Intellectual protection of the discovery that blood glutathione can be a biomarker for screening asymptomatic patients at risk for heart failure has been fostered through a patent in 2010.

Assessment of the team's organisation and life

Although the team is very large, it has an excellent management system with yearly career planning meetings for all individuals in the group; scientists in the group are very happy with their level of independence (3 emerging groups); management is open and transparent.

The committee notes that there is a high (and still increasing) percentage of permanent staff engineers in this team, which may be beneficial to the management. The team leader clearly succeeded in maintaining a common strategy for the group. The organization of research has been conceived to bring together MDs, biologists and scientists with complementary expertise in order to have the best chance for successfully conducting the three major research objectives: i) defining the genetic and clinical spectrum and the natural history of NMDs; ii) investigating pathophysiological mechanisms of gene mutations that induce skeletal or cardiac muscle damage; iii) developing innovative therapeutic approaches. Several common topics (contractile dysfunction, mechano-transduction, apoptosis/autophagy, fibrosis…) are addressed transversally through pooling specific expertises (nucleus, extracellular matrix, contractile proteins, cellular trafficking…).

The Committee has been impressed by the remarkable ability of the team leader to incubate emerging talented scientists who will have the capacities to become independent team leaders.

Assessment of the team's involvement in training through research

The three group leaders of the team have graduate students (conferring Masters and doctoral degrees) who have been first authors or co-authors of 2-3 articles. The team leaders give lectures to graduate students in various French and German programs centered upon myology and neuromuscular disorders.

Of concern, there seems to be a drastic reduction (from 4 to 0) in the number of post-docs, without any increase in the number of PhD students (3 for 4 HDR). It is recommended that the team attract new post-docs or more Ph.D students (2 PhD students at the time of the visit) for continued training and transmission of their knowledge and expertise.

Assessment of the five-year plan and strategy

This team has a relevant strategy from clinical research to translational medicine, through the identification of disease-causing genes or modifiers, and a comprehensive characterization of the underlying pathological mechanisms.

Each project is clearly established and led by highly competent investigators who are funded and who submitted additional grant applications in Jan-Feb 2013.

The team has developed new tools to test gene-based therapies, and has established relevant local and international collaborations to pursue its investigations through the curative modulation of MAPK pathways in laminopathies and autophagy/apoptosis in collagenopathies. The graft of ALDH+ progenitors with increased cardiomyogenic differentiation abilities seems promising in dilated hearts of LMNA models animals and may open important perspectives in the specific treatment of cardiomyopathy in L-CMD patients.

Conclusion

Strengths

The team has extremely well developed national and international networks.

The projects encompasses a very effective continuum from clinical description to pathomechanisms and promising preclinical trials.

The team represents an example in terms of effective translational research for a disease, a lead in the overall goal of the centre.

Weaknesses or threats

With 3 emerging groups and PIs, the team leader will have to anticipate the remodeling of its human resources by both enrolling new young researchers and keeping an attractive environment and a continued interaction with these emerging groups.

Recommendations

The high level of expertise of the team in several retractile myopathies should help them focus on the molecular pathways underlying early-onset pathomechanisms emerging from longitudinal studies. Such projects should also benefit from the inclusion of high throughput analyses to be launched in parallel, so that new unexpected actors and pathways could bolster the presently established morbidity map.

Team 2 :

Pathophysiology and Therapy of Dynamin 2-related centronuclear myopathy

Name of team leader:

Mr Marc BITOUN

Workforce:

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions			
N2: Permanent researchers from Institutions and similar positions	2 [2]	2 [2]	2
N3: Other permanent staff (without research duties)	1 [1]	1 [1]	1
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)			
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	2 [2]	1 [1]	1
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6	**5 [5]**	**4 [4]**	**4**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	0	
Theses defended		
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions		

• Detailed assessments

Assessment of scientific quality and outputs

The main goal of the team is to characterize the genetic and pathophysiological bases of several forms of centronuclear myopathies (CNM). Presently, the proposed team is a spin-off group from Team 1 composed of two researchers (1 CR1, the team leader; 1 CR2 recruited in 2010, both from INSERM), a permanent research assistant and 1 post-doctoral fellow.

In the past 5 years, the team has been especially active in increasing the genotype-phenotype correlation map of autosomal dominant forms of CNM, underlying the wide-spectrum of clinical manifestations. By using proprietary cell lines and a Knock-in humanized mouse models that recapitulate most clinical signs and histopathological features described in patients, the team focused on essential pathophysiological mechanisms leading to CNM, selected because they were conserved in patients and mutated mice. The mechanisms studied include those contributing to calcium homeostasis, membrane trafficking (endocytosis and internal trafficking), and autophagy.

Scientific productivity over the last 5 years has been quantitatively below the average of the Unit, with 11 publications since 2007, for 2 ETP (6,3 compared to 6,6; number of publications per author, corrected for the position of the authors), but qualitatively very good with 30% of their publications in the top 10% most cited and published in journals such as Science, Hum. Mol. Genet. or Traffic, and 80% of their production above the median for citations, reflecting the overall originality and visibility of the results obtained by the team.

Assessment of the team's academic reputation and appeal

This team, responsible for a landmark 2006 paper in Nature Genetics on dynamin 2, is well implanted in national and international consortia associating clinicians, pathologists, diagnostic and research laboratories. The team leader has established and curates an international mutation database that provides clinicians and scientists with relevant genotype-phenotpe data on AD-CNM, an essential tool for future clinical trials. The group leader has been invited to several international and national meetings.

The team has been funded by an Emergence-UPMC program and a Myotubular Trust research grant. An improved international visibility, through a better identification of the group as an independent emergent team, should help the team obtain the additional external funding that will be required to cover its increasing needs.

Assessment of the team's interaction with the social, economic and cultural environment

As part of Team 1, the team has been active in the social dissemination of the research activities through direct interaction with patients' families such as at the “Journées des Familles” or the "Université AFM maladies rares", organized by the AFM. Because the team is emergent, its interactive contribution will have to be evaluated after the next 5-year program.

Like most teams in the Myology Research Center, an important part of their mission is to be involved in disseminating information to patient groups and transfer of knowledge.

Assessment of the team's organisation and life

As this group is just being formed, it is not feasible to assess its “organization” and integration in the present unit.

Assessment of the team's involvement in training through research

The team leader has not yet obtained his HDR. As the group just formed, its level of training of students cannot be evaluated.

Assessment of the five-year plan and strategy

The team is proposing to study the physiological role of membrane trafficking in muscle function, formation, in maintenance and function of triads, in AAV vectors nucleo-availability, as well as deciphering how DNM2 gain-of-function induces alterations in this trafficking, eventually leading to CNM.

In addition, therapeutic strategies for DNM2-related CNM are envisaged, through specific spliceosome-mediated RNA trans-splicing of the mutated RNA or through the non-specific modulation of genes controlling muscle mass.

Overall, the project seems ambitious with respect to the present size and financial support of the team and focusing on the most promising outcomes (the organizing role of endocytosis in wild type and CNM muscle cells) is advisable.

However, relevant collaborations have already been set up and preliminary encouraging results have been obtained. The scientific strategy for the next 5 years will thus have to be adjusted as per the successful recruitment of post-docs and PhD students into the team.

Because the team's achievements will be highly dependent upon both the interface with patients and an easy access to state-of-the-art crucial biotechnologies, insertion of team members within the proposed "Research Center for Myology" appears highly relevant. There is clearly a potential for specific synergistic activity between this team and team 9, with which a closer interaction would help reach a more reasonable size and international visibility through the aggregation of their members' recognized skills.

Conclusion

Strengths

The project is well positioned in an emerging field.

The team is a world leader in DNM2-related myopathies and successfully contributes to the developing field of membrane trafficking mechanisms underlying development, growth and maintenance of muscles.

Weaknesses

The emerging team has not yet gained significant recognition and may be fragile in its autonomy. Only only one post-doc and no PhD students in the team as of July 2012 to Feb. 2013. The PI needs to rapidly obtain his HDR degree and recruit at least one Ph.D student.

Recommendations

Presently, the four members of the team share space, equipment and accomodations with other teams from the Center. A management strategy will have to be set up to maintain opportunities resulting from the existing synergistic links with other teams of the Centre, while developing internal strengths within the team.

In particular, there is an apparent complementarity between this research and that proposed by team 9. There is potential for synergistic activity with the closer interaction of the two groups.

The ambitious project would benefit from focusing its objectives and developing privileged interactions with team 9.

Team 3 : Regeneration, Pathophysiology & Therapeutic Approaches: Cellular Models

Name of team leader: Mr Vincent Mouly

Workforce:

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	3 (0,6)	3 (0,6)	3
N2: Permanent researchers from Institutions and similar positions	6 (6)	6 (6)	6
N3: Other permanent staff (without research duties)	1 (1)	1 (1)	1
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)			
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	4 (4)	3 (3)	3
N6: Other contractual staff (without research duties)	4 (4)	4 (4)	0
TOTAL N1 to N6	**18 (15,6)**	**17 (14,6)**	**13**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	3 => 3	
Theses defended	6	
Postdoctoral students having spent at least 12 months in the unit	11	
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	7	6

• Detailed assessments

This team was one of the two large groups in the unit during the previous evaluation period. It continued to develop over the last years and is composed of internationally recognized experts on human muscle satellite cells and human myogenic progenitors. The overall objective of this unit is to gather expertise from human muscle cell biology in order to increase the understanding of fundamental and therapeutic approaches for numerous muscular dystrophies.

Assessment of scientific quality and outputs

This team is internationally renowned and serves as a reference in the field of human muscle cell culture and the development of biologically useful myoblast cell lines. Many lines have been derived for specific muscle diseases (listing but a few examples; DMD, OPMD, Myasthenia Gravis, LGMD1C, LGMD2B, nesprin deficiency, CMD, SMA or FSHD). The cells lines produced are instrumental to therapeutic advances and cellular modelling of muscle disease. The team has disseminated these lines on a collaborative basis to over 70 international groups.

The work developed by this team provides an essential service and tool to the scientific community at the crossroads of fundamental cell biology and therapeutical strategies. These cell lines are also used by many investigators in the Institute, making the work of the team very important for the overall objectives of the institute.

Scientific publications are many, with a proportion in collaborations because of their contributions of reagent production. The team has published over 50 manuscripts in peer-reviewed journals since 2008, including high standard papers published as co-authors from collaborations. These manuscripts have been published in journals such as Molecular Therapy, Am. Journal of Pathology, Human Molecular Genetics, J. Biol. Chemistry, Aging Cell, and Journal of Cell Science, amongst others, attesting to the very good quality of the science.

Assessment of the unit's academic reputation and appeal

The team leaders are well reputed experts in their field. The reagents produced by this team (immortalized and differentiatable myoblast cell lines) are used world-wide by investigators working in the area of Muscular Dystrophy research. The team has been open to numerous collaborations with internationally renowned laboratories in Ireland, USA (Washington DC), Nantes, Denmark and Leiden (Netherlands). In addition, it is clear that a major strength of this team is the internal collaborative role it plays at the institute level. The down side from this broad collaborative involvement is that a driving thematic research area of the team may be less clear.

The team leaders have a large international visibility, being invited to international meetings, serving as session chairs, giving seminars in London, Washington, Berlin, Barcelona... The ex-leader of the team has taken up enormous administrative and scientific responsibilities within the field.

Assessment of the unit's interaction with the social, economic and cultural environment

The team is well organized in terms of patient groups and knowledge transfer. They are involved in collaborations and funding in numerous transnational programs such as EU networks and the MYOAGE network. They also bring an important participation to pharmaceutical industries (FIOCRUZ Institute, Benitec, Biophytis, Shire, Servier, SANOFI or PTC) and in the filing of patents, all evidence of the lab's recognized research and its ability to establish and development useful cell models. The cell lines that they produce are instrumental for both therapeutic advances and cell biological modelling and understanding.

Assessment of the unit's organisation and life

Excellent management. The team has been very efficient in terms of permanent staff recruitment, very high promotion of young scientists with proof-of-principle favouring the emergence of new team leaders such as new team 4 which was incubated as part of this team.

Assessment of the unit's involvement in training through research

They have trained numerous PhD students and post-doctoral fellows. This team is being seen by the institute Director as an incubator to train people working in the field of neuromuscular disease. The team leaders also have a large implication in teaching at the Masters level and in organizing training courses. Considering the high number of HDRs in the team and the number of "sub-thematic" groups in the team, more Ph.D students could be enrolled.

Assessment of the five-year plan and strategy

The team proposes a set of 3 goals 1) to decipher and model human muscle regeneration towards understanding ageing and dystrophic conditions; 2) to unravel the pathophysiological mechanisms in fascioscapulohumeral dystrophy (FSHD) and oculopharyngeal muscular dystrophy (OPMD) at the cellular level ; and 3) Optimize cell therapy for skeletal and cardiac muscles. These objectives are feasible within the next funding period. The experts involved in these aims are excellent and some of the proposed work will be done in collaboration with other teams in the unit as well as with numerous labs around the world.

The projects are well justified, sound and the techniques state of the art. Scientifically, there are very few concerns in term of feasibility.

The ALDH activity as a marker for progenitor cells is good, but determining the threshold between ALDH-high and -low cells is arbitrary and may lead to results that are difficult to standardize or reproduce.

Also, various muscle cell populations have been tested for cardiac repair, and some of these populations are being investigated in the clinic. As such, it will be of interest to extend the analysis of ALDH expression to these muscle-derived cell populations with a high regeneration capacity in the heart.

The team proposes important but quite diverse projects. The breadth of the group is extremely wide but to gain in international impact, it would be important to select and deepen some specific aims.

Conclusion

Strengths

A large team, convincingly led by recognized experts in the field of human muscle cell biology.

Extremely good international reach and visibility as well as good management and training of young scientists. The team has grown considerably over the last five years and has fostered the emergence of new young teams. The strength of this team is, without any doubt, in their expertise in producing critical human cell lineages, and in their their training portfolio which also brings an essential component to the whole unit project.

Weaknesses, Threats

The large size of the team added to the heavy administrative and scientific coordination charges taken up by the leaders may bring difficulties in keeping the transmission to young scientists at its best. The wide array of directions foreseen in the project may be narrowed for an in depth analysis of selected original findings.

Recommendations

To gain in scientific impact, it will be important to structure and prioritize specific objectives.

In particular, the strength on each project will be reinforced by further comparative analyses and characterization of immortalized- versus primary human myoblasts and diseased- versus healthy muscle-derived cells, in addition to the development and sharing of the cell lines themselves.

Team 4 : Pathophysiology & Biotherapy of Myotonic Dystrophy

Name of team leader: Mr Denis FURLING

Workforce:

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	1 (0,5)	2 (0,6)	1
N2: Permanent researchers from Institutions and similar positions	2 (2)	3 (3)	2
N3: Other permanent staff (without research duties)	1 (1)	1 (1)	1
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)			
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	1 (1)	1 (1)	1
N6: Other contractual staff (without research duties)	1 (1)	1 (0,5)	
TOTAL N1 to N6	**6 (5,5)**	**8 (6,1)**	**5**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	2 => 1	
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken	1	
Qualified research supervisors (with an HDR) or similar positions	1	4

• Detailed assessments

Assessment of scientific quality and outputs

The overall goals of Team 4 are 1) to decipher the molecular mechanisms through which the splicing defects lead to particular DM1 muscle phenotypes; and 2) to develop therapeutic strategies to abolish the cellular toxicity induced by the mutant DMPK expanded CUG transcript.

Scientific productivity over the last 5 years has been quantitatively and qualitatively excellent with publications in journals such as Nature Structural and Molecular Biology, Nature Medicine, and PNAS, as senior or co-senior author. The team has also made a major advance linking one of the mis-spliced genes in DM1 to a clinical phenotype (muscle weakness). It is important to know that such links have only been made for four other mis-spliced genes in DM1. This collaborative effort was published in Nature Medicine. It is clear that this is a perfect time for the group to evolve into a new team which will fit in well with the translational theme of the proposed Centre.

Assessment of the unit's academic reputation and appeal

Although the group is emerging as a new team, it is well recognized in the field of myotonic dystrophy research. The group is very active in promoting the visibility of the host institution, especially in France. The PI coordinates a French DM network and participates to two international DM networks including a European E-Rare (ERA-Net for research programs on rare diseases) consortium. The Group collaborates with several investigators who are very well recognized internationally. Overall, the academic reputation of this new team can be considered to be very good.

Assessment of the unit's interaction with the social, economic and cultural environment

The Group has been active in the social dissemination of research activities in the field of muscular dystrophies in the public media (newspapers, television, radio), as well as via the AFM “Journees des Familles”, etc. The Group has been particularly active in fostering appropriate intellectual protection of their discoveries. The PI has been invited to give presentations worldwide, and is clearly recognized for his contributions to the field.

Assessment of the unit's organisation and life

Not applicable for a young emerging team.

Assessment of the unit's involvement in training through research

The Team includes PhD and Masters students. The scientific activities carried out by the group offer an excellent scientific environment for education of undergraduate and postgraduate students.

Assessment of the five-year plan and strategy

Excellent long-term design and promising program for fundamental understanding and therapeutic advances in repeat-associated diseases. Appropriate collaborations have been established. A good sense of conservativeness will benefit these early achievements.

Conclusion

Strengths

Overall, this is an emerging but yet very strong team, with already established international visibility and a promising program for the future. The team brings a strong basis both in basic and translational research in DM1.

Weaknesses

None to report specifically for this emerging group

Recommendations

Keep on with the good momentum and interaction with the other teams

Team 5 : RNA-Repair based Therapeutics & Skeletal Muscle Pathophysiology

Name of team leader: Ms France PIÉTRI-ROUXEL

Workforce:

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	1 (0,5)	1 (1)	1
N2: Permanent researchers from Institutions and similar positions	5 (5)	3 (3)	3
N3: Other permanent staff (without research duties)	6 (6)	3 (3)	3
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)			
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	4 (4)	3 (2,15)	3
N6: Other contractual staff (without research duties)	2 (1,5)	1(0,5)	0
TOTAL N1 to N6	**18 (17)**	**11 (9,65)**	**10**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	6 => 1	
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit	3	
Number of Research Supervisor Qualifications (HDR) taken	3	
Qualified research supervisors (with an HDR) or similar positions	6	4

• Detailed assessments

The overall goals of the original team, from which team 5 is emerging, were to develop innovative molecular therapies for neuromuscular disorders, particularly based on RNA repair. Team 5 currently comprises around 12-14 persons, with 1 PU-PH, also the Director of the Centre, 1 CR1 (who is responsible for the leadership of the team), 2 CR, 3 research assistants and 2 technicians. The non-permanent staff includes 2 post-docs, 1 PhD student and 2 Master students. Four senior researchers conduct at least one of the 5 objectives presented in the research project.

Assessment of scientific quality and outputs

Team 5 members have a longstanding interest in neuromuscular disorders, including clinical and experimental pathophysiology, mutation-specific repair strategies, development of appropriate tools to monitor disease progression and therapeutic interventions (mandatory for human applications), optimization of pre-clinical experiments and finally, conduction of clinical trials in patients.

Excellent advances in exon skipping-based therapeutic applications have been carried out under the direction of the previous group leader. Publications in the best journals and 10 patents were produced. Over the last 4 years, the team has been quite active in generating tools to achieve molecular correction in small and large animal models of muscular dystrophies as well in understanding some of the molecular correlates hampering successful application of the developed strategies in vivo. In particular, work on a modified snRNA U7-based constructs to modulate alternative splicing using AAV vectors in a large DMD animal model (the GRMD dog) is state-of-the-art and deserves rapid clinical transition.

This team has filled a total of 10 patents in the last four years.

Taking into account the publications of the previous, larger, team, scientific productivity has been quantitatively and qualitatively very good; (30 articles of which several articles with senior authorship in Human Molecular Genetics and Embo J. for example) in the last five years, with 74% of their production above the median for citations and 23% of their publications in the top 10% most cited, with 14 articles (40%) in the IF top 10 and an average IF around 6.6.

Assessment of the unit's academic reputation and appeal

The group is well recognized in the field of repair strategies based on exon skipping for muscular dystrophy (particularly for the common and devastating Duchenne muscular dystrophy) as well as for being a protagonist in muscle molecular biology. Senior researchers are very active in promoting the visibility of the host institution, not only in France but also in Europe. The PI coordinates the International Collaborative Effort for DMD (ICE project); one of the group members coordinates an international PhD course with joint activities with the University of Berlin, Germany.

The team is actively involved in several high-level scientific networks (particularly in the field of exon-skipping), collaborates with investigators who are very well recognized internationally, and several members are regularly invited to participate to conferences, cutting-edge events, scientific expertise and editorial activities. This is particularly the case for the ex-group leader and for one member of the present group who is also Director of the Centre. He has been actively involved in the organization (including as President) of several International Congresses of Myology throughout the world and has considerable implication in professional memberships, editorial boards and scientific councils in the field of NMDs. This Director is both the PI of ongoing phase 2 studies for exon 51 skipping, the leader for the exon 45 skipping programme starting in 2013 and a EU FP7 WP leader for the morpholino-exon 53 skipping consortium.

Assessment of the unit's interaction with the social, economic and cultural environment

The team is active in the social dissemination of research activities in the field of muscular dystrophies in the public media (newspapers, television, radio), as well as via interactions with family associations. Results and concepts are regularly disseminated to the public and several members of the emerging team 5 regularly participate to national and international family meetings. The Group has been particularly active in fostering appropriate intellectual protection of their discoveries. Members have contributed to 8 patents since January 2009; they have developed appropriate strategic partnerships with pharma industry as well as the hospital for clinical trials. High dissemination of knowledge has also included the creation of a biotech spin-off.

Assessment of the unit's organisation and life

Team 5 is an emerging team that emanated from the previous team: "Biotherapies for Neuromuscular disorders" after the departure of its leader to the University of Versailles. The emerging team has undergone significant restructuring with this departure of the former group leader (together with 6 members of the group). Members of the emerging team have strong and complementary expertise in the field of mRNA repair, muscle function, clinical knowledge of disease and management of clinical trials.

Although their remarkable efforts towards therapy (particularly for DMD) must be encouraged, the size of the team now appears under-estimated for carrying out the 5 different ambitious objectives planned in the project. With the high number of researchers with HDR still in the group, recruitment and training of Ph.D students is recommended.

Assessment of the unit's involvement in training through research

There has been a tradition of high level training of PhDs as well as post-docs in the previous team from which the present team is emerging. The team has had significant involvement in national and international PhD programs as well as in the teaching/training including Summer Schools, Medical and Master programs. The Director of the Centre has largely contributed to the creation and funding of the 2010-2015 MYOGRAD program offering close to 40 stipends for PhDs or MD-PhDs.

Assessment of the five-year plan and strategy

The project proposed for the next five years is, at least in part, a direct continuation of the previous activity but also includes a set of new investigations. The approach to induce correction of DMD mutations by trans-splicing (Objective 1) is molecularly attractive, however, this is hampered by a low probability of success, especially considering the difficulties that other investigators have had in this area since the late '80s, when the trans-splicing concept was first aired. The major problem of this approach relates to its relative inefficacy when applied to animals. Thus, should the group wish to pursue this further, specific efforts should be devoted to enhancing in vivo efficacy.

Another objective that would possibly benefit by being reconsidered is Objective 3, focused on characterizing the fate of AAV vectors in dystrophic skeletal muscle. The experiments proposed, aimed at visualizing entry and intracellular routes of viral particles, are outdated and recapitulate experiments already widely performed by other investigators in various experimental settings. The project would benefit by being more innovative in dissecting pathways using genomic functional approaches (e.g. siRNA screenings or other large scale, high throughput techniques).

The most exciting part of the proposal is Objective 5, aimed at optimizing pre-clinical AAV-based gene therapy for DMD using a U7-AAV skipping construct in the GRDM dog.

Conclusion

Strength and opportunities

This team brings to the Centre a unique expertise in clinical trial protocols and patient assessment and management of neuromuscular disorders in close collaboration with the major European networks coordinating cutting edge therapies in these disorders.

Weaknesses and threats

The team has undergone unforeseen restructuring with the departure of several scientists, the committee has raised the point that conducting five highly competitive objectives in parallel may represent a weakness.

Recommendations and conclusion

It may be advisable that this team identifies a lead project, in order to prioritize their research efforts. The group maintains a strong potential but would benefit greatly from reinforced leadership, in terms of visibility. The capacity to realize this success will depend on appropriate re-structuring of the group.

Team 6 : CNS Gene Transfer & Biotherapy of Motor Neuron Diseases

Name of team leader: Ms Martine BARKATS

Workforce: 9

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions		1 (1)	
N2: Permanent researchers from Institutions and similar positions	1 (1)	1 (1)	1
N3: Other permanent staff (without research duties)	2 (2)	2 (2)	2
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)			
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	2 (2)	2 (2)	0
N6: Other contractual staff (without research duties)	3 (3)	3 (3)	2
TOTAL N1 to N6	**8 (8)**	**9 (9)**	**5**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	1=> 0	
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit	4	
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	1	2

• Detailed assessments

Assessment of scientific quality and outputs

The research activity of this emerging group is primarily focused on the development of biotherapies for MN diseases (MND) such as spinal muscular atrophy (SMA) and amyotrophic lateral sclerosis (ALS) through the development of efficient gene transfer methodologies based on AAV vectors for gene transfer in the central and peripheral nervous system. The team has been interested in developing vectors that cross the blood brain barrier (BBB) upon systemic vector administration. Work was performed on a mice animal model of ALS and in a cat model of SMA. Although the approaches undertaken have not been particularly novel, the experiments performed have led to the observation that some of the AAV vectors utilized have the capacity to cross the BBB and could thus be potentially amenable to clinical development for systemic administration. The team also maintains active collaborations with other groups in the field of molecular genetics of neurodegenerative disorders.

Good publication level with 9 articles in peer-reviewed journals of which 4 as senior author and excellent technology transfer in terms of patents. Scientific production includes high quality research papers in well-ranked speciality journals (Annals of Neurology, Hum Mol Genet, Mol Ther) and four patents.

Assessment of the unit's academic reputation and appeal

The group leader is internationally known for her contributions to the development of AAV vectors and their use in the nervous system. The Team appears particularly active in the gene therapy field. Despite limited conceptual innovation in the performed studies and attempts to explain the observed properties of AAV vectors, the activity has significant application potential. The group has the potential to broaden its international collaborations and scientific impact. Several invitations in international conferences since 2008.

Assessment of the unit's interaction with the social, economic and cultural environment

The Group is very well funded, especially through patient charities and associations. It has received independent funding (ANR, AFM, ARS, SMA Europe).

Four patents that are key to the use of AAV vectors in CNS diseases have been granted. The PI has been rather active in protecting the intellectual property of the Group’s discoveries. In this respect, however, the commercial utilization of AAV9-based vectors might infringe upon the already existing patents covering the use of this serotype.

Commendably, the PI pays due attention to promoting scientific research in a social context in the media and with the families of affected patients, in order to raise public awareness of neuromuscular disorders.

Assessment of the unit's organisation and life

There is clear and important potential for increased interactions and collaborations both with in house teams and with researchers outside the centre. At the time of the visit, the PI had no HDR and the team seemed to have no Ph.D students; the defense of an HDR by the PI and the recruitment and training of new students should therefore be a priority.

Assessment of the unit's involvement in training through research

The team is composed of 9 members: 2 post-docs, 3 engineers (1 is preparing a PhD thesis), 2 technicians. An assistant professor will join the team in early 2013. Of note: Team 6 is the only team which includes more engineers and technical staff (5) than researchers (4, including post-docs).

It is strongly recommended that the team leader obtain her HDR degree in 2013 and recruit at least one Ph.D student. At the moment, she has supervised several MSc students and 1 PhD student (co-supervision).

Assessment of the five-year plan and strategy

The group aims to exploit the AAV vectors it recently developed. Given the size of the group, many projects are proposed and although most involve collaborations, it seems ambitious. The main objectives of the group are to develop efficient methods for widespread gene transfer into CNS cells, including spinal cord MNs and to validate the potential of these methods for gene therapy in mouse and large animal models of ALS and SMA. In the long term, the group aims to translate successful research to preclinical and clinical development. Finally, the group plans to develop gene therapy strategies for other CNS disorders as part of collaborative efforts.

The proposed five year plan is intensely focused on exploring various aspects of gene therapy for SMN and ALS, especially in small animal models, as well as on understanding some of the genetic features of SMN. The project appears generally well planned. It includes finding the optimal therapeutic window for SMN gene transfer and the optimal in vivo site for SMN protein expression, as well as a series of optimizations in AAV vector design, dose, route of delivery and preclinical biodistribution and toxicology studies. Although not particularly exciting or innovative, this type of study is nevertheless required to achieve future clinical application. Some other aspects of the proposed research, however, are less clear. The choice of the BAG1 antiapoptotic factor, or the Neurovita axonal growth promoting factor, or Myostatin inhibitors to improve efficiency of SMN gene delivery is not justified. There might be dozens of other factors that could be considered as alternatives. A more systematic, rational approach would possibly be more appropriate.

The ALS part of the project is less developed, less organized and less sound. For example, why does the Group use “artificial miRNAs” to target mutant SOD1, instead of an siRNA targeted against the mutated mRNA? How would the expression of this miRNA be achieved inside the cells – miRNA are usually expressed as natural precursor sequences? RNAi silencing of mutated alleles has already been broadly attempted by other investigators in other settings, so far with limited success, and the proponents should be aware of the technical limitations of this approach.

Focusing the whole project on SMN gene therapy would possibly strengthen the proposal.

Conclusion

Strength and opportunities

The group has a unique expertise in AAV vector development for CNS applications. This creates many opportunities for collaboration, developing therapies for neuronal diseases. There is a good potential for translation of the SMA project to the clinic.

Weaknesses and threats

This is a group mainly oriented on technological development and translational research. It is therefore important to consider the patents produced and the key role of the group in the production of crucial tools for gene therapy in the nervous system when analyzing their scientific production.

Recommendations

It would be better to focus the project on the SMA gene therapy aspect. The ALS project being less well developed could be left on the side. Focusing the whole project on SMN gene therapy would strengthen the proposal.

At the time of the visit, the team seemed to have no Ph.D students; the recruitment and training of new students should therefore be prioritized.

The committee feels that there is important potential for increased interactions by the team, both within the unit and with scientists in other units on site such as the ICM (Institut Cerveau Moelle).

Team 7 : Myasthenia Gravis: Etiology, Physiopathology & Therapeutical Approache

Name of team leader: Ms Sonia BERRIH-AKNIN & Ms Rozen LE PANSE

Workforce:

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	0		
N2: Permanent researchers from Institutions and similar positions	2 (2)	2 (2)	2
N3: Other permanent staff (without research duties)	2 (2)	3 (3)	2
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)			
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	6 (6)	5 (5)	6
N6: Other contractual staff (without research duties)	1 (1)	2 (2)	1
TOTAL N1 to N6	**11**	**12**	**11**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	1 => 0	
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit	5	
Number of Research Supervisor Qualifications (HDR) taken	0	
Qualified research supervisors (with an HDR) or similar positions	2	2

• Detailed assessments

Assessment of scientific quality and outputs

The group has published several important original findings during the evaluation period; these publications have focused on acetylcholinesterase splice variants in myasthenia, CCL21 expression and thymic hyperplasia in myasthenia, thymic remodeling, role of SDF-1 in recruitment of peripheral blood cells to the thymus of myasthenia patients and most recently, on the role of mesenchymal stem cells in indirectly inducing tolerogenic monocytes.

Very good level of publications with 20 publications since 2008, of which 10 with the team leader as senior author; studies have mainly been published in good speciality journals including Immunobiology, J Cell Sci, Stem Cells, Eur J Immunol, Autoimmunity and Blood, amongst others.

Important contribution to providing information on the natural history of myasthenia gravis with significant implications in organizing networks.

Assessment of the team's academic reputation and appeal

The group of the team leader has been extremely successful in coordinating EU and international grants during the past 4 years. She has coordinated FP5 and FP6 grants entitled EUROMASTHENIA and MYASTAID and is presently coordinating a EU FP7 grant entitled FIGHT-MG. The work of the group leader has been highly cited in the myasthenia field. The group has contributed to federating different international laboratories working on myasthenia during the past 15 years

The group leader has also organized meetings in Paris as well as co-organized a meeting on Treg/Tolerance in Jerusalem.

Assessment of the team's interaction with the social, economic and cultural environment

The team has made a significant investment in the transfer of information on myasthenia gravis to professional and patient organizations. They have developed a website <http://www.euromyasthenia.org/> in order to promote understanding of the disease and have interacted extensively with patient organizations. They have contributed to important diffusion of information on myasthenia gravis to the public with publications of newsletters for patients and their families.

Assessment of the team's organisation and life

The team was part of Inserm U966 in Clamart during the 2008 evaluation and joined the present unit in 2010.

One scientist in the unit was recruited to a CR1 CNRS position in 2007. In addition to the two senior scientists, the group consists of 5 postdocs, 3 research assistants, 1 PhD student and 1 project manager.

It will be important to assess the integration of the team within the Myology Institute and with the other teams in the institute and to strengthen the cohesion and leadership of the group.

Assessment of the team's involvement in training through research

There is presently 1 PhD student in the team. Several other students have been co-supervised (notably with teams at the Technion Institute, Israel). The second senior scientist in the team has apparently not yet obtained her HDR, a degree required for the supervision of PhD students in France.

The group has also trained M1 and M2 students and designed guides to aid MDs in the evaluation and treatment of patients with Myasthenia.

Although they have trained 2 PhD students, the team presently has no Ph.D students and it is highly recommended that they enroll new doctoral students.

Assessment of the five-year plan and strategy

It will be important to strengthen the immunological expertise in the group in order to best carry out mechanistic studies. Potential interactions with Team 10 should promote the collaborative productivity of this group.

Conclusion

Strength and opportunities

The group has been a major international leader in federating laboratories studying myasthenia gravis. They also have very successfully managed EU networks. This creates opportunities for collaboration and translation of projects to the clinic.

Weaknesses and threats

Many of the studies proposed by the group would benefit from a more mechanistic approach in order to promote their international visibility in the pathogenesis of MG. The focus on mesenchymal stem cells as a therapeutic option for the treatment of MG would benefit from interactions with the clinical facilities presently planning clinical trials.

Recommendations

Increased interactions with group 10 will benefit the immunological expertise of the group. It will also be important to clarify the structure of the group in terms of the proposal to be headed by two co-directors.

Team 8 : Development & Stem Cells

Name of team leader: Mr Frédéric RELAIX

Workforce:

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	
N1: Permanent professors and similar positions			
N2: Permanent researchers from Institutions and similar positions		3 (3)	
N3: Other permanent staff (without research duties)		2 (1)	
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)			
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)		2 (2)	
N6: Other contractual staff (without research duties)		0	
TOTAL N1 to N6		**7**	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	2	
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	1	1

• Detailed assessments

Assessment of scientific quality and outputs

The team was founded as an AVENIR team and during the previous evaluation period, it was part of the "Myology group" unit housed at the UPMC building.

Exploiting a large collection of transgenic and mutant mice, the team works on the mechanisms of skeletal muscle stem cell specification and the role of Pax3/7 during development, post-natal stages and aging, and analyzes potential links with cell cycle regulators as well as alveolar rhabdomyosarcoma, a rare form of cancer involving translocation of Pax3 or 7. In particular the team has recently shown that myogenic differentiation is restricted by neural crest cell lineage via neuregulin signalling during development (published in Dev Cell with the group leader as senior author). The group has also been very productive in terms of original results published in collaboration with renowned scientists in the field with more than 30 publications co-authored with groups in Institut Pasteur, Institut Cochin and in London.

Assessment of the team's academic reputation and appeal

Excellent visibility in the field with multiple invitations to national and international meetings

The team collaborates productively both with groups from the myology center as well as with internationally renowned scientists in the field of muscle cell development.

A patent has been issued based on their results and they are involved in several well-funded EU and other networks.

The team has been able to attract good quality post-docs and the work they propose to continue will benefit from their collaborations with labs around the world.

Assessment of the team's interaction with the social, economic and cultural environment

The group leader is part of many networks and is a member of a LabEx on stem cells. He also has written several well cited reviews with renowned scientists in the field and has filed a patent on the identification of a muscle specific regulatory element.

Assessment of the team's organisation and life

Localizing the team in the same physical location with the other groups in the unit will clearly foster improved interactions and further develop "in house" scientific collaborations and the evolution of their research program.

Assessment of the team's involvement in training through research

The group leader has trained one student, without resulting publication(s) and one student in the group has a second author manuscript in revision (Development).

Assessment of the five-year plan and strategy

All of the proposed projects represent the continuation of ongoing research and are well supported by an appropriate collection of transgenic mouse models. One of the strengths of this team lies in the array of mutant mice that they have developed and are at their disposal. This provides the team with unique tools to perform the work proposed. However, it is also a potential weekness as the animal facility in the building is very limited and has more than reached saturation.

For one of their aims, addressing the cellular origin of rhabdomyosarcoma, the proposal would be strenghtened by including investigations of blood vessel derived progenitors such as pericytes or mesoangioblasts, as they have been described as one potential source of adult stem cells and vascularization is also relevant in cancer development.

As for their further studies on the roles of Pax3 and Pax7 in the specification and activation of satellite cells, the team has well developed models in the murine system. The team is in a unique environment with access to human muscle samples and accompanying expertise, and it is therefore suggested that the team also considers comparative analyses of the expression and role(s) of Pax3 (and Pax7) in human muscles and muscle pathologies.

Conclusion

Strengths and opportunities

The strength of this team lies in its expertise in the development and use of a large collection of mice models. They have already proven they are well placed to exploit these models. Their opportunity, like all teams in the IM, is their unique environment where they have a privileged access to human muscle samples from healthy and specific diseases donors, and a platform with expert pathologists that can help them to best analyze human tissue material.

Weaknesses

The animal facility available at the moment in 105 Bd de l'hopital is clearly not sufficient for the mouse models used and needed by this group.

The training of doctoral students is one of the weaker points in the activity of the team.

Recommendations

The team should expand its well-advanced expertise and questions to the domain of human muscle progenitor cells, an area in which they can collaborate efficiently with very good teams in the myology center.

Team 9 : Cytoskeleton Architecture & Cell Polarization

Name of team leader: Mr Edgar GOMES

Workforce:

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions			
N2: Permanent researchers from Institutions and similar positions		2 (2)	
N3: Other permanent staff (without research duties)			
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)			
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)		4 (3,1)	
N6: Other contractual staff (without research duties)			
TOTAL N1 to N6		**6 (5,1)**	

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students	1	
Theses defended	1	
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions	1	1

• Detailed assessments

The cell nucleus is positioned at specific places within the cytoplasm in muscle cells and fibers, and this position is important in different cellular, development and pathological processes. The goal of the team is to identify molecular mechanisms of nuclear positioning and to understand the role of nuclear positioning in different myogenic cellular events. The studies are performed in two different situations: 1) nuclear positioning during cell migration 2) nuclear positioning during myofiber formation.

Assessment of scientific quality and outputs

The team has developed cutting edge methods for tracking nuclei during cell migration and myotube formation. Using candidate gene approaches and siRNA based screens they have identified new players in nuclear positioning and produced outstanding results published in high visibility journals. The productivity and output of the group is outstanding. As a young group leader, the PI has proven his capacity to undertake forefront research, lead and direct a group at the highest level. The research achieved to date has shown a clear capacity to examine intellectually challenging questions, pose realistic research objectives and publish original observations in the highest cited journals, such as in Nature, Embo report and J. Cell Science as senior author, and Science or Nature Cell Biology, in collaborative publications.

Since its creation in 2007, the team has opened a new area of investigation and positioned itself at the leading edge of the field.

Assessment of the unit's academic reputation and appeal

The team has rapidly gained an international reputation and an excellent attractivity. It has developed collaborations with outstanding national and international groups. The team has attracted several foreign PhD students and 4 postdocs. The group leader is regularly invited to international meetings.

Assessment of the unit's interaction with the social, economic and cultural environment

Funding is secured and comes from various sources (AFM, ANR, ARC, Ligue contre le cancer). Collaborations with the best groups at the international level are already effective. The work of the team is focused on the understanding of fundamental cellular mechanisms that occur during development, cell migration and muscle regeneration. Since these mechanisms are required for the normal function of these cells and tissues and some of them are already known to be disrupted in multiple pathologies. This work will provide the basis for the development of new therapies to ameliorate or correct multiple muscle disorders, in particular centronuclear myopathies.

Assessment of the unit's organisation and life

Strong interactions with many other groups have improved understanding of specific muscle diseases and potential translational applications. The team has been productively involved with teams 2 and 3.

The team is hosted in a large ‘open lab’ space. All standard equipment for molecular, cell and animal system biology is present on site as well as access to platforms at the University. New culture facilities house all necessary culture hoods, incubators, etc. Appropriate space for radioactive work and darkrooms is also available. Several fluorescence microscopes, including an inverted confocal microscope with 4 laser lines, and three inverted epifluorescence microscopes equipped with an XY stage, live-imaging chamber are available. One of the inverted microscopes is equipped with a microinjection system and another is equipped with a FRAP-photoactivation system with 3 laser lines.

Assessment of the unit's involvement in training through research

Since 2008, the team has hosted one Master 1 student and 3 Master 2 students (one from the Erasmus program). One foreign PhD student is currently hosted. The group leader participates in teaching at the national and international levels (teaching at the Master’s level in Paris 5 University and in the mycology summer school of Paris, teaching in the Myograd program in Berlin, courses in PhD program in Portugal, International Cell Biology course of Institut Curie in Paris).

Assessment of the five-year plan and strategy

The projects of the group are based on their identification of new players in nuclear positioning. The team will also develop studies related to muscle membrane movements and further characterize the links between nuclear positioning and global cellular organization. The group has very good complementarity with some teams working on specific myopathies in the institute; it should be highly encouraged to continue collaborating in that respect. The team leader is encouraged to choose 2-3 research objectives in order to unravel the mechanistic bases underlying their observations.

Conclusion

Strengths and opportunities

The team has an outstanding scientific production and has developed cutting edge live imaging technology.

Weaknesses and threats

The team is physically located apart from the teams with which it collaborates within the institute of Myology. Solutions should be rapidly found to regroup these teams in the same building.

Recommendations

The team has an excellent and ambitious project. The project leader has the opportunity to extend his study to human muscle cells and human muscle pathologies by closely interacting with other teams in the unit.

Team 10 : Inflammatory muscle and targeted innovative therapy

Name of team leader: Mr Olivier BENVENISTE

Workforce:

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014	2014-2018 Number of project producers
N1: Permanent professors and similar positions	0	2 (0,6)	2
N2: Permanent researchers from Institutions and similar positions	0	4 (0,6)	3
N3: Other permanent staff (without research duties)	0	0	
N4: Other professors (Emeritus Professor, on-contract Professor, etc.)	0	1 (1)	
N5: Other researchers from Institutions (Emeritus Research Director, Postdoctoral students, visitors, etc.)	0	0 (0)	
N6: Other contractual staff (without research duties)	0	2 (2)	
TOTAL N1 to N6	**0**	**9**	**5**

Team workforce	Number as at 30/06/2012	Number as at 01/01/2014
Doctoral students		4
Theses defended		
Postdoctoral students having spent at least 12 months in the unit		
Number of Research Supervisor Qualifications (HDR) taken		
Qualified research supervisors (with an HDR) or similar positions		3

• Detailed assessments

Assessment of scientific quality and outputs

The various members of the group have all published important studies during the past evaluation period but as this group did not exist as an entity per se, they do not represent the specific output of the present group. The group leader focused his efforts mainly on inclusion body myositis as well as other myosites and in a second axe, invested significant efforts in circumventing the immune response against viral components as well as therapeutic proteins expressed in clinically used gene therapy vectors. The manuscripts resulting from this research have been published mainly in specialty journals. Important papers include the results of a phase I gene therapy trial for limb girdle muscular dystrophies using an AAV1-gamma sarcoglycan vector and a critical study on the natural history of inclusion body myositis (both published in Brain).

Assessment of the team's academic reputation and appeal

The group leader has been invited to multiple meetings including 5 outside of France during this evaluation period, and has been involved in 3 workshops (with 1 as the organizer). As indicated below, the group leader co-directed an international workshop to define diagnostic criteria and outcome for inclusion body myositis (IBM).

The other senior members of the team have also been heavily involved in running clinical trials and have all been invited to speak at international meetings. One foreign member due to join and co-direct the team has clear international visibility in the field of gene therapy, and particularly as relates to immunogenicity.

Assessment of the unit's interaction with the social, economic and cultural environment

The group is made up largely of hospital physicians and its goal is to perform translational research, bringing basic research to clinical trials. They are associated with several clinical trials in inflammation/biotherapy in the context of the DHU (hospital-university department).

The study of the team on IBM has resulted in new guidelines for the treatment of this disease.

The team also interacts extensively with the Genethon division focusing on gene therapy trials and will be involved in the immmunomonitoring of the upcoming AAV1-CMV-SERCA2 gene therapy trial for heart failure.

The team has also been an international leader in defining the natural history of inclusion body myositis and has obtained an Inserm/clinical grant to perform a clinical trial assessing the effect of rapamycin on muscle strength in this disease.

Assessment of the unit's organisation and life

The group leader was previously part of a team entitled "Tolerance-Autoimmunity-Transplantation" at the UPMC. In the context of the present evaluation, he is now forming his own team in the Myology Research Center. This team will be co-directed with another team leader who has just joined the unit from the University of Pennsylvania. Six other medical personnel are part of the group (3 PH and 3 PU-PH).

As this group is just being formed, it is not feasible to assess its “organization” and integration in the present unit. However, the team seems to have good interactions with many of the other groups in the unit, including groups 2, 3 and 7.

Assessment of the unit's involvement in training through research

There are presently 3 PhD students in the team (1 is an MD fellow). It is not clear whether any of these students have defended their theses during the evaluation period. The group has also supervised 4 M2 students (not clear as to the unit in which these students were present).

The head of the group organizes a teaching module for the faculty and has taught in two DIU as well as in a summer school of myology.

Assessment of the five-year plan and strategy

The research of the group will be focused on several aspects; establishing patient group databases for myositis diseases, defining the “immunome” of patients with myositides and dystrophies, developing cell culture and animal models to determine the links between inflammation and muscle degeneration, and continuing their involvement in clinical trials. Another aim, to be directed by the incoming co-director, is to develop new strategies aimed at overcoming cellular and humoral immunity to AAV vectors, and evaluate the saftey of these new approaches in small and large animal models.

Conclusion

Strengths and opportunities

The potential interactions between the present group leader and incoming associate professor will have significant impact in strengthening the contributions of this group to solving some of the immunological bottlenecks in clinical gene therapy applications.

Weaknesses

There may be an unbalance between a large number of researchers implicated in clinical research and responsibilities; and a very limited number of experienced researchers involved in fundamental "bench research".

Recommendations

It will be important to rapidly integrate this team and confirm the recruitment of the incoming co-director, to establish a cohesive research strategy. The rapid recruitment of good post-doctoral researchers is advisable.

5 • Conduct of the visit

Visit dates:

Start:	Monday 18th February 2013 at 8:45
End:	Tuesday 19th February 2013 at 17:45

Visit site:	Site hospitalier la Pitié-Salpêtrière
Institution:	Institut de Myologie, Bâtiment Babinski
Address:	Avenue Vincent Auriol, Paris 75013

Conduct or programme of visit:

Day 1, 18th February 2013

08:45 - 09:10	Closed meeting: Committee and Scientific Delegate
09:10 - 10:00	Thomas VOIT: introduction, presentation of the Centre for Myology: Structure, topics, vision
10:00 - 10:40	Ms Gisèle BONNE: team 1
10:40 - 11:10	Mr Marc BITOUN: team 2
11:10 - 11:40	Coffee break
11:40 - 12:20	Mr Vincent MOULY: team 3
12:20 - 12:50	Mr Denis FURLING: team 4
12:50 - 14:00	Lunch, discussion with project leaders
14:00 - 14:30	Ms France PIÉTRI-ROUXEL: team 5
14:30 - 15:00	Ms Martine BARKATS: team 6
15:00 - 15:40	Ms Sonia BERRIH-AKNIN & Rozen LE PANSE: team 7
15:40 - 16:15	Coffee break
16:15 - 16:50	Mr Frédéric RELAIX: team 8
16:50 - 17:20	Mr Edgar GOMES: team 9
17:20 - 17:50	Mr Olivier BENVENISTE & Federico MINGOZZI: team 10
17:50 - 18:20	Mr Thomas VOIT: transversal axes of the Centre
18:30 - 19:10	meeting of the committee with all the group leaders
19h30 - 21:00	Dinner buffet with all the team and group leaders

Day 2, 19th February 2013

08:45 - 09:45	Split Committee meetings: Meeting 1: with staff researchers Meeting 2: with PhD students and post Docs Meeting 3: with engineers, technicians & administrative staff (ITA's)
09:50 - 10:30	Committee meeting with trustees (meetings held in absence of the Director and team leaders)
09:45 - 11:00	INSERM/CNRS representative separate meeting with ITA's
10:30 - 11:00	Coffee break
11:00 -11 :30	Committee meets with Director of Centre
11:30 - 14:15	Closed meeting (boxed lunch) of the Committee and Scientific Delegate
14:00 - 14:30	Committee meets Mr Serge UZAN
14:30 - 17:30	Closed meeting of the Committee and Scientific Delegate
17:30 - 17:45	End of the visit, coffee/tea break

Specific points to be mentioned :

Ms Joelle AMÉDÉE-VILATMITJANA was unable to attend the visit.

6 • Statistics by field: SVE on 10/06/2013

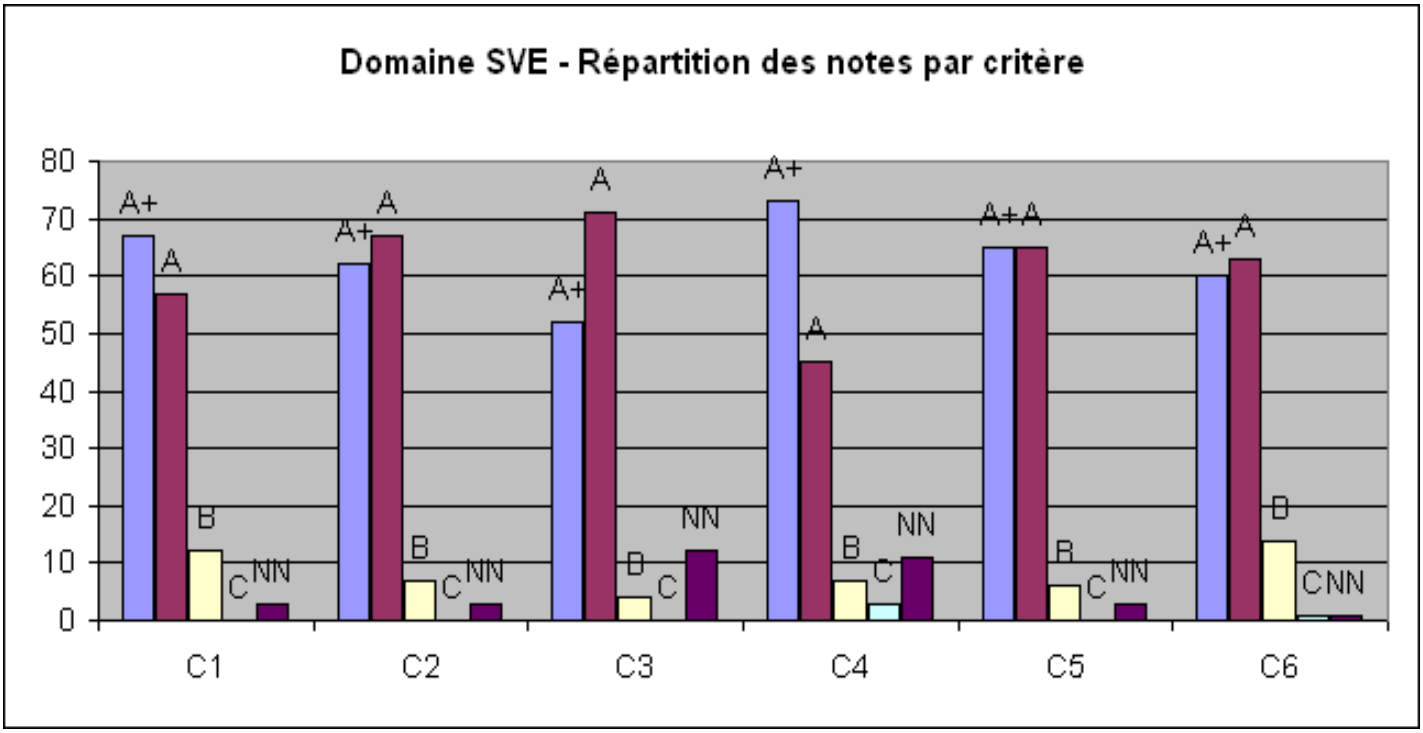
Grades

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	67	62	52	73	65	60
A	57	67	71	45	65	63
B	12	7	4	7	6	14
C	0	0	0	3	0	1
Non Noté	3	3	12	11	3	1

Percentages

Critères	C1 Qualité scientifique et production	C2 Rayonnement et attractivité académiques	C3 Relations avec l'environnement social, économique et culturel	C4 Organisation et vie de l'entité	C5 Implication dans la formation par la recherche	C6 Stratégie et projet à cinq ans
A+	48%	45%	37%	53%	47%	43%
A	41%	48%	51%	32%	47%	45%
B	9%	5%	3%	5%	4%	10%
C	0%	0%	0%	2%	0%	1%
Non Noté	2%	2%	9%	8%	2%	1%

Histogram



7 • Supervising bodies' general comments

Paris le 19 04 2013

Le Président
Didier Houssin
Agence d'évaluation de la recherche
et de l'enseignement supérieur
20 rue Vivienne - 75002 PARIS

M. le Président,

Nous avons pris connaissance avec le plus grand intérêt de votre rapport concernant le projet du Centre de recherche en myologie, porté par M. Voit. Nous tenons à remercier l'AERES et le comité pour l'efficacité et la qualité du travail d'analyse qui a été conduit.

Ce rapport a été transmis au directeur du laboratoire qui nous a fait part en retour de ses commentaires que vous trouverez ci-joint. Nous espérons que ces informations vous permettront de bien finaliser l'évaluation du laboratoire.

Restant à votre disposition pour de plus amples informations, je vous prie de croire, M. le Président, à l'expression de mes salutations respectueuses.

Le Vice -Président Recherche et Innovation

Paul Indelicato

Vice-présidence Recherche et Innovation
Tél. 01 44 27 20 09
www.upmc.fr

Response to AERES report for the unit : Research Center for Myology

The members of the Research Centre for Myology application appreciate the constructive review by the AERES committee and would like to thank the Committee for its efforts.

The response will be in two parts:

1) General comments
2) Comments regarding each team

General comments

-Spatial situation: We gratefully acknowledge that the AERES Committee agrees to our SWOT analysis that the current spatial distribution of the research groups on two buildings is a major threat and hindrance. To overcome this situation the Dean of the Medical Faculty, Pr. Serge Uzan, has promised to unite all research teams of the future Centre in the 105, Bd de l'Hôpital building within the next two years.

-Partial dependence on AFM funding: On one hand we would like to emphasize that the AFM/AIM funding is also a strength of the future Research Centre. In particular, it helped us to compensate for the near-complete absence of ITA positions from the EPST grant giving bodies. Furthermore, the ambitious translational programmes could not be run without this funding. On the other hand, while we agree that alternative funding through IP valorisation takes time, we are currently negotiating licences/commercial exploitation for 8 of the patents submitted since January 2009 indicating that this is more than an abstract plan.

-Assessment of the unit's academic potential: The unit has obtained a fifth EU FP7 grant, SCOPE-DMD (T. Voit, WP-leader, team 5).

-DHU label obtained: The future Research Centre is structural and integral part of the DHU (Département Hospitalo-Universitaire) project MAMUTH (MAladies MUsculo-squelettiques et THérapies innovantes) granted in 2013 (project leaders: T. Voit and R. Vialle). This project will provide a labelled framework for the first University Hospital Department for the treatment of muscle diseases in France.

Comments regarding each team

Team 1, Ms. Gisèle Bonne

Factual correction:

> Old Team Workforce table
>
> **N5** Other researchers from institutions (Emeritus Researcher Director, Postdoctoral Students): Number as at 01/01/2014 ~~=1~~; 2014-2018 number of project producers ~~= 0~~.
>
> New Team Workforce table

N5 Other researchers from institutions (Emeritus Researcher Director, Postdoctoral Students): Number as at 01/01/2014 = 2; 2014-2018 number of project producers = 2.

- Postdoctoral researchers and PhD Students: team 1 has launched two new PhD projects within MYOGRAD for the next university year (2013-214). There will be in January 2014, two postdoctotal researchers in the team and salaries for three additional postdoctoral researchers are currently requested in the recent grant proposals submitted by the team members and still under evaluation.

Team 2, Mr. Marc Bitoun

- HDR and PhD students: The procedure to obtain HDR was initiated by Marc Bitoun. The registration form was submitted at the UPMC (UFR 927 – Commission Sciences de la Vie) in March 2013. HDR will be defended in 2013. Thereafter, a project will be submitted at the “école doctorale – complexité du vivant” (ED515) in order to recruit a PhD student in 2014.

- Interaction with team 9 (Edgar Gomes): We agree with the committee that there is potential for specific synergistic activity with the closer interaction of our two groups. Privileged interaction will be strengthened through several common actions. An ANR project (ANR blanc 2013) was recently submitted, including the two groups, which will allow development of a common project on the biogenesis and maintenance of T-tubules and sarcoplasmic reticulum in congenital myopathies. To allow closer interaction, joined monthly meetings will start in September 2013 with the members of the two teams, and students, co-directed by M. Bitoun and E. Gomes, will be recruited in order to start collaborative studies.

Team 3, Mr. Vincent Mouly

In response to the recommendations, team 3 will focus its efforts on 3 specific programs :
- Cell to cell interactions via the secretomes and secreted vesicles
- Pathophysiology and therapeutic strategies for OPMD and FSHD
- Myogenic and cardiac progenitors expressing ALDH.

Regarding this last aim, we agree that the sorting of ALDH+ cells on the unique basis of brightness would be difficult to standardize. In our work, however, since we observed that ALDH+ / CD34- cells were the most efficient regarding myogenesis in vitro and in vivo, the progenitors from skeletal and cardiac tissues will be identified and sorted on the double basis of ALDH and CD34 expressions. These populations and their differentiation capacities are under study and are subject to a patent application at the moment. In a clinical perspective, we also develop approaches to sort the cells that would not be solely based on cytofluorimetry, because this methodology is difficult to set up in the clinical practice.

- PhD students: team 3 has launched two new PhD projects within MYOGRAD and has submitted another PhD project to ED 515.

Team 4, Mr. Denis Furling

Factual correction:

Old: Assessment of the unit's academic reputation and appeal

Although the group is emerging as a new team, it is well recognized in the field of myotonic dystrophy research. The group is very active in promoting the visibility of the host institution, especially in France. ~~The PI coordinates the International Collaborative Effort for DMD (ICE project); one of the group members coordinates an international PhD course with joint activities with the University of Berlin, Germany~~. The Group collaborates with several investigators who are very well recognized internationally. Overall, the academic reputation of this new team can be considered to be very good.

New:

Although the group is emerging as a new team, it is well recognized in the field of myotonic dystrophy research. The group is very active in promoting the visibility of the host institution, especially in France. The PI coordinates a French DM network and participates to two international DM networks including a European E-Rare (ERA-Net for research programs on rare diseases) consortium. The Group collaborates with several investigators who are very well recognized internationally. Overall, the academic reputation of this new team can be considered to be very good.

Team 5, Ms. France Piétri-Rouxel (M. Thomas Voit)

Factual correction:
- Team workforce table: number of Research Supervisor Qualifications (HDR) taken: noted: zero correct: one (Thomas Voit)
- Assessment of the unit's academic reputation and appeal: T. Voit has just obtained a further EU FP7 grant (SCOPE-NMD) as workpackage leader for a 2-OH-methylOAS phase 1-2 treatment trial.

-Leadership: The recommendation is appreciated and M. Thomas Voit will lead the team. Ms. Piétri-Rouxel has submitted her HDR, the defence is planned for September 2013. She will co-direct the team.

-Students and HDR: Once Ms. Piétri-Rouxel (HDR pending) and Ms. Stéphanie Lorain (HDR will be submitted in 2013) have obtained their HDR PhD students will be recruited. Thomas Voit currently has two PhD students, but as he was hitherto affiliated to team 1 (G. Bonne) these students are listed under this team. Both already have publications and are set to submit their thesis 2013/2014.

-Re-focussing the objectives:

We agree that the 5 objectives are wide and propose to refocus as follows:

- We will drop trans-splicing (objective 1). Our own work *in vivo* shows that the current efficiency of trans-splicing is too low to guarantee real therapeutic effects for dystrophin (MS in revision with NAR) and for MYBP3 (MS submitted to Mol Ther).
- We will focus on three topics: 1) optimizing dystrophin rescue, including mini-dystrophin, and its biochemical and functional properties; 2) Characterizing and optimizing the fate of AAV-mediated genomes in dystrophic muscle. To the best of our knowledge there is no published data on this subject. We have submitted a first MS describing, for the first time, that AAV-U7 genomes are more rapidly lost from dystrophin-deficient tissue, and also how to remedy to this loss (Mol Ther, submitted). We agree that cutting edge technology is needed to further characterize this problem and have submitted a grant request using deep sequencing to investigate aspects of this question. 3) Optimizing the pre-clinical setup for AAV-mediated exon skipping and microdystrophin gene therapy, and implementation of the first gene therapy trial for DMD.

Team 6, Ms. Martine Barkats

-Commercial use of the patents: The patents taken do not infringe upon existing patents covering the AAV 9 serotype. Commercial use (i.e. freedom to operate) exists at Généthon through licensing. In contrast, our patents will limit the freedom to operate for third parties who want to use this serotype for CNS or eye therapy.

-HDR and students: 1 PhD student is currently in the team (T. Marais). The PI will submit her HDR in 2013. Yan Clement MCU who joins the team in 2013 has an HDR. After his arrival further PhD students will be recruited.

-Collaborations: Important collaborations exist with the ICM (Institut du Cerveau et de la Moelle epinière – Alexis Brice on Spinocerebellar ataxia 7) and with the Institut de la Vision (José Sahel on retinal degeneration) as well as with Necker Hospital (Catherine Caillaud) on lysosomal diseases.

-Clarification of strategy: The choice of BAG1 and Neurovita relies on their dual role in apoptosis inhibition and interaction with the inhibitory Rho kinase signalling pathway which is dysregulated in SMA cellular and animal models.

-Increasing focus: The team will focus the project on SMA gene therapy and collaborate for other diseases of the CNS or neuromuscular system. It will not pursue the ALS project as a focus.

Team 7, Ms Sonia Berrih-Aknin

Please find factual corrections or clarifications in the following paragraphs:

1- Factual corrections

- The committee reported "The team was part of Inserm U966 in Tours during the 2008 evaluation and joined the present unit in 2010".

In fact, the team was part of **Inserm U996 in Clamart** during the 2008 evaluation and joined the present unit in 2010".

- The team does not have an administrative assistant.

2- Clarifications and Responses

- At the present time, we have 1 PhD student and 2 master students. We totally agree with the recommendation of the committee and we are in the process of enrolling another PhD student.

- Surprisingly, in the section "Assessment of the five-year plan and strategy" nothing is stated regarding the five-year project. As described in the document submitted for the AERES evaluation, our project aims to better understand the pathophysiological mechanisms of MG, to elucidate the pathogenic events involved in their initiation and chronicity, and to propose new therapies for MG patients, namely by the use of mesenchymal stem cells. For this therapeutic option, the tools have been successfully developed and as stated by the committee, interaction with Team 10 will facilitate the development of the clinical trial.

- The proposed nomination of Ms. Rozen Le Panse as co-director is based on the following reasoning:
  Rozen Le Panse has joined the team 12 years ago and is responsible for one aim of the project. She will submit her HDR in 2013.
  In the next evaluation session (2018), Sonia Berrih-Aknin will not be allowed to lead the team, because of the age limit. To anticipate the future, the proposition of the co-direction is to progressively transfer the responsibilities from SBA to RLP.

Team 8, Mr. Frédéric Relaix

A second HDR has been recently obtained in the team recently, and additional PhD students will be trained in the team.

Team 9, Mr. Edgar Gomes:

Efforts will be made to increase the interactions between team 9 and the rest of the teams located in a different building. New joint lab meetings and journal clubs between team 9 and team 2 will be set up to foster the exchange of knowledge and overcome the problems that arise from being in different buildings.
Team 9 will extend its work to human cells and pathologies studied by other teams of the center. As an example, team 9 obtained recently funding from E-RARE to investigate ALS and will take advantage of the knowledge and materials from human samples that exist in the center.

Team 10, Mr. Olivier Benveniste

We fully agree with the suggested recommendations and we just would like to clarify few points on our project, to show that we already anticipated some of the possible limitations of our team and implemented actions that are part of the Commission's recommendations.
While we agree that our team is mostly composed by researchers implicated in clinical research, we believe that this is also a key strength for our consortium, since this expertise is important to achieve the overall goal of curing muscle diseases through translational research. Nevertheless, in order to increase the number of experienced researchers involved in fundamental "bench research" in our team, we have already taken the following measures:

1. Recruited a post-doc, expert in fundamental research, starting 1st of April 2013.

2. Developed a strategy to rapidly integrate the incoming co-director Federico Mingozzi (who is a fundamental researcher with a clear international visibility, as outlined by the commission)
    a. The co-director will present his HDR this year
    b. The co-director will candidate for the next EPST exam to get a tenured statutory position
    c. The co-director (as Principal Investigator) just received the Marie Curie Career Integration Grant on his project within the team (Awarded 100 000 euro over 4 years (2013-2017)).
    d. The co-director already submitted the following grants, which are completely in line with the team project:

- NIH SBIR grant on Immune tolerance induction in Pompe disease. 300 000 dollars (2013-2015). Role: Consultant and collaborator
- Bayer Early Career Grant. Humoral Immunity to AAV. Letter of intent accepted, full submission submitted. 200 000 dollars (2013-2015). Role: Principal Investigator.
- E-rare - Hemorare. Gene therapy for hemophilia A. Letter of intent accepted. 300 000 euros (2013-2016). Role: Co-Principal Investigator.
- EMBO Young Investigator Award. Submitted material for first phase. 60 000 euros/year for 4 years + various support (2013-2017). Role: Principal Investigator.
- ERC consolidator grant - MoMAAV. Immune responses to AAV.
- Submitted 1 750 000 euros (2014-2019). Role: Principal Investigator.
- PLUStem. Letter of intent submitted. Develop AAV for gene and cell therapies. 600 000 euros (2014-2017). Role: Co-Principal Investigator.
- Italian Ministry of Research. Gene therapy for AMD. 400 000 euros. Letter of intent accepted, full submission sent. (2014-2017). Role: foreign partner.
- Vaincre les Maladie Lysosomiales. Immune response in Pompe disease. Submitted letter of intent. 100 000 (2013-2015). Role: co-Principal Investigator.
- Beckton Dickinson Immunology. Immune responses to AAV. Submitted. Provides research reagents. (2013). 30 000 euros. Role: Principal Investigator.

We believe that this approach, in addition to our project presented to the commission, will foster the growth of our emerging new team and constitute the backbone of our cohesive research strategy.

On behalf of the members of the future Research Centre for Myology I wish to express my hope that you will find these responses constructive and to the point regarding the questions raised.

I am of course available for any further questions you may have.

Paris, 17.4.2013

Sincerely,

Pr. Thomas Voit