Report from the visiting committee

Research unit: Therapy of striated muscles disorders

University of Paris 6

April 2008
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The research unit:

Name of the research unit: Therapy of striated muscles disorders
Requested label: UMR CNRS, UMR_S INSERM

N° in case of renewal:
Head of the research unit: M. Thomas VOIT

University or school:

Université Paris 6

Other institutions and research organization:

INSERM, CNRS

Date(s) of the visit:

February 12th 2008
Members of the visiting committee

Chairman of the committee:
M. Laurent SCHAEFFER, Lyon

Other committee members:
M. Kevin P. CAMPBELL, Iowa City IA, USA
M. Ulrike MAYER, Norwich, UK
M. Peter W. J. RIGBY, London, UK
M. Stefano SCHIAFFINO, Padova, Italy
M. Volker STRAUB, Newcastle upon Tyne, UK

CNU, CoNRS, CSS INSERM, représentant INRA, INRIA, IRD..... representatives:
M. Catherine BISBAL, Montpellier, CoCNRS representative
M. Claude FERE, Brest, CSS Inserm representative
M. Laurent LESCAUDRON, Nantes, CNU representative

Observers

AERES scientific representative:
M. Bruno GASNIER

University or school representative:
M. Jean CHAMBAZ, Université Paris 6

Research organization representative(s):
Mme Martine DEFAIS, CNRS
Mme Chantal LASSERRE, INSERM
Report from the visiting committee

1. Short presentation of the research unit

- Numbers of lab members: 62, including
  - 6 researchers with teaching duties
  - 14 full-time researchers from INSERM or CNRS
  - 9 full-time researchers from Association Institut de Myologie
  - 8 engineers (including 2 paid on grants)
  - 15 postdocs
  - 18 PhD students, all with a fellowship
  - 10 technicians and administrative assistants
- Number of HDR: 17; number of HDR who are PhD students advisors: 9
- Numbers of PhD students who have obtained their PhD: 22
- Average length of a PhD during the past 4 years: 3.5 years
- Numbers of lab members who have been granted a PEDR: 1
- Numbers of “publishing” staff researchers with or without teaching duties: 29 out of 29

2. Preparation and execution of the visit

9:00-9:45 Public presentation of the unit ‘Therapy of Striated muscles disorders’ by the director
9:45-10:15 Public presentation of group 1 by the group leader
10:15-10:45 Public presentation of group 2 by the group leader
11:00-11:30 Public presentation of group 3 by the group leader
11:30-12:00 Public presentation of group 4 by the group leader
12:00-12:30 Public presentation of group 5 by the group leader
12:30-13:15 Lunch break and discussion between the Committee, Director and team leaders, administrative representatives
13h15-13h45: meeting of the committee with the group leaders
14h00-14h30: coffee in the hall of the Institute of Myology with all students, ITA/IATOS, post-docs
14h30-15h30: visit of the Laboratories: Physiology, U 582
15h30-16h45: The committee splits in groups to meet with the research teams.
16h45-18h45: committee deliberation
18h45: Debriefing by the president of the committee
3. **Overall appreciation of the activity of the research unit, of its links with local, national and international partners**

**General comments:**

The site of the Pitié-Salpêtrière hosts two laboratories working on skeletal muscle: Unit 1 (“Myology group”, UMRS787) at the 105 bd de l’hôpital and Unit 2 (“Therapy of Striated muscles disorders”) in the Babinsky building, on the other side of the hospital. Given the obvious complementarity between these units, they were evaluated on two consecutive days by the same committee with the exception of two experts present on either February 11th or February 12th.

The unit “Therapy of Striated muscles disorders” corresponds to the evolution of the U582 of the Institute of Myology. With the reorganization of research centers currently going on in the hospital of the Pitié-Salpêtrière, part of the historical groups of the Institute of Myology dedicated to the heart will join the future “heart center”, and two groups studying the neuromuscular junction or mitochondrial diseases proposes to join the future “Institut du cerveau et de la moelle”. Three new groups will be created in the Institute of Myology, groups 2 and 3, which are still affiliated to unit 1, and group 5 which will be located in Germany. Groups 1 and 4 were former groups of U582. The unit is very active in terms of national and international collaborations. It is involved in several European networks and is funded by many sources including ANR and AFM. All the groups have an international reputation and collaborate with renowned groups throughout the world.

A general comment concerning the organization of the unit is the size of the groups, which are quite large. This is in part due to the nature of the unit, oriented towards pathologies and therapy that usually involves larger staffs than fundamental research groups. The group leaders and the director argue that it facilitates the management, but the committee raised the issue that such structures could preclude the emergence of talented young independent scientists, or incite them to leave the unit. This has for example been the case for group 4 of Unit 1. However, it is fair to mention that most of the staff scientists of this unit do not wish to gain further independence.

Another particularity, and an interesting initiative of this unit, is that each of the four resident teams is responsible of a common technical platform, related to their activity and know how.

The Unit has a strong collaboration with the large animal platform of the veterinary school and the CEA-AIM NMR platform.

4. **Specific appreciation team by team and/or project by project**

**Team 1: Genetics and Pathophysiology of Neuromuscular Disorders**

This team is composed of 21 persons, with four senior researchers in charge of their own projects (1 DR2 INSERM and 3 CR1 INSERM), 3 permanent research assistants and 6 associated MDs. The non permanent staff is composed of 4 post docs, 2 research assistants, 1 PhD student and 1 master student. The team is very well funded (FP6 STREP, ANR, AFM, INSERM, Leducq foundation...). This team is dedicated to the study of the genetics and pathophysiology of specific neuromuscular disorders.

Four main topics are supervised by the four senior researchers with common goals: 1) define the genetic, clinical spectrum and natural history of the neuromuscular disorders they study, 2) investigate the pathophysiological mechanisms involved in order to 3) propose and test therapeutic approaches. The team is responsible for the histopathology platform. In addition to the supervision of the team, the team leader coordinates the work on laminopathies (induced by mutations in the lamin A/C gene) of striated muscle. This group is at the world leading edge of laminopathies. It has structured a whole network and database on the topic and constitutes an impressive example of successful translational research. The second senior scientist
mutations in neuromuscular disorders in 2002. This subgroup also provides an example of excellent translational research. Clinical trials are at hand. The third senior scientist (CR1) is in charge of the study of centronuclear myopathies. The group has previously identified mutations in the Dynamin 2 gene in patients with centronuclear myopathy. The team is now focusing on the characterization of the pathophysiological mechanisms. Therefore, collaborations with group 3 of unit 1 will be extremely fruitful and should be reinforced. The fourth senior researcher (CR1) studies the pathophysiological mechanisms of contractile dysfunctions. 3D culture models will be further developed to characterize interactions with the extra cellular matrix. To analyse contractile function at the molecular level actin-myosin interactions will be studied using in vitro motility assays. This subgroup develops efficient tools to study contractile function, but should push its studies to go beyond models. Collaborations exist with group 4 of unit 1.

Overall the scientific production of the team is very good, that of the team leader being excellent. The team has been associated to excellent scientific papers in Aging Cell (2007), Journal of Clinical Investigation (2007), New England Journal of Medicine (2006), Nature Genetics (2005). They are also very collaborative as illustrated by their association to numerous collaborative papers.

Team 2: Remodeling, Regeneration and Cell Therapy of Striated Muscle

Team 2 is composed of 7 permanent researchers (2 INSERM DR1, 3 CRNS CR1, 1 UPMC assistant professor and 1 AIM researcher), 2 associated MDs, 3 non permanent research assistants, 6 post doctoral fellows, and 9 students (7 PhD and 2 EPHE). This team is responsible of the culture platform. Part of the team is mainly dedicated to the platform and should be identified as such. The team leader currently leads a team in unit 1, and the future team in unit 2 will be composed of the current team plus two teams of U 582. The team will be directed by the current leader of the group of unit 1, in close association with the four other project leaders. The team is focused on remodelling, regeneration, and cell therapy of striated muscle. The group is very well funded (AFM, INSERM, UPMC, ANR) and is involved in four European networks. The team has a longstanding experience in the study of muscle cell progenitors proliferation, aging and transplantation for therapeutic purpose. They are more and more extending their work towards in vivo models, which will be beneficial for their publication level. Since 2007, the team has raised its publication standards, and they are willing to keep this line. They recently published in Aging Cell interesting results on the role of telomerase and cdk4 in alleviating muscle progenitors senescence. Part of the team is working on Dystrophic Myotonia 1 and have generated valuable results by microarray analysis of RNA splicing in DM1 muscles that will provide pathophysiological mechanisms to explain the features of DM1 muscles, and should be published in an excellent journal. Finally, the team has many collaborations with excellent groups throughout the world. The team is also actively involved in translational research, especially for cell transplantation. They are already involved in phase I clinical trials to test autologous myoblast transplantation in post-ischemic cardiac insufficiency, Oculopharyngeal muscular dystrophy and Facioscapulohumeral muscular dystrophy.

Team 3: Biotherapies for Neuromuscular Diseases

Team 3 was initially located at Genethon and is currently hosted by Unit 1. It comprises 7 researchers (2 CNRS CR1, 1 INSERM CR1, 4 AIM researchers), 7 engineers and technicians, and 3 post docs. It will be joined by another group of Genethon (one researcher, one postdoctoral fellow, and two technicians). The team is in charge of the molecular biology technical platform. The main axis of the team is the development of gene therapy approaches based on exon splicing to treat dystrophinopathies. For therapeutic developments, the team works in close collaboration with the veterinary school of Maison Alfort that hosts GRMD dogs. Exon skipping can be beneficial to many neuromuscular disorders, some of which will be investigated in collaboration. The team also focuses on the study of the pathophysiology of muscle dystrophies, in particular on the mechanisms of adipose metaplasia. Finally, the role of myostatin in muscle homeostasis is also investigated. The team leader is at the world leading front for Duchenne Muscular Dystrophy treatment. DMD is an ideal model system to demonstrate the pertinence of the efficiency of the exon skipping approach, and the committee felt that given the leading position of the team in this field, it was important that the team kept to concentrate the main part of its efforts towards this goal to remain at the top front. The study of the role of myostatin in muscle homeostasis is also a very competitive topic, and although the project of the team on myostatin is very good, the team is in a less favourable position at the international level on this topic. The part of the team that will join team 3 to develop work on motor neuron diseases will benefit from the expertise of the team to develop AAV-based exon skipping approaches to address motoneuronal diseases. Conversely, team 3 will benefit from the expertise of this subgroup to study the presynaptic compartment, although this
subgroup is not at the same level of excellence as the current team. Team 3 is very well funded (UPMC, INSERM, AFM, ANR, ICE, European networks). The team has collaborations with Team 2 and with top groups in the world and its scientific production is excellent. Two patents have been produced.

Team 4: Physiology and in vivo evaluation of biotherapies

Team 4 is dedicated to physiological evaluation. It comprises 14 members (1 MD PhD team leader, 1 professor of Université Paris V, 1 principal investigator AIM, 3 AIM researchers, 2 post doctoral fellows, 2 PhD students, 3 clinical investigators and 1 quality specialist. This team has developed a unique array of physiological tests ranging from electrophysiology and cardiovascular evaluation to NMR imaging (in collaboration with the CEA-AIM NMR platform). This team greatly participates to create a unique environment in Europe to develop and evaluate muscle biotherapies. Its activity is developed in close contact with the other teams, and specific developments are implemented according to the needs. Overall, the impression of the committee is that this team performs an outstanding routine and development work as a platform, and would therefore benefit to be considered as such. This would rationalize evaluation, which is excellent for a core facility, whereas it is rather average when scientific production is considered for a research group.

Team 5: Functional genomics of familial hypertrophic cardiomyopathy

Team 5 is composed of 7 persons (1 CNRS research director, 2 post-docs, 3 PhD students, and 1 technician). The team studies functional genomics of familial cardiac hypertrophic cardiomyopathy. Its major objective is the elucidation of the mechanisms by which cardiac myosin binding protein C mutations cause the disease. The scientific strategies proposed are very good, and the proteasome approach is original. The background of the team is very strong on genetic analysis, and the committee encourages the leader to develop collaborations with cell biology groups for its pathophysiological studies. The research theme of this team constitutes a good link between research on skeletal and cardiac muscles. The team is very well funded (FP6-Marie Curie excellence grant, Leducq foundation, and important German grants). The scientific production of the team is excellent and it is involved in several collaborations within the unit and with strong international groups. The particularity of this group is to be localized in Hamburg, which will clearly not facilitate close contacts with other teams of the unit. The hosting laboratory in Hamburg develops excellent work on heart tissue evaluation and therapy, and particularly renowned for its work in the field of heart tissue engineering. However, the reasons that justify a localization in Hamburg rather than a classical collaboration should be more clearly defined. The committee proposes that such a decision should not rely on a single team leader, but should rather result from a concerted negotiation between the universities (UPMC and Hamburg), which could for example serve as a basis to develop student exchange programs.

5 • Appreciation of resources and of the life of the research unit

- Of the quality of the management:

The choice of this unit is to have few large teams, with several senior researchers in each teams placed under the responsibility of the team leader. For the viability of the structure, care will have to be taken that the researchers in charge of a theme continue to be given their due position on the publications they produce. The director is aware of this point and proposes to discuss these issues during the meetings of the laboratory council. The director has decided to dedicate his time to the management of the unit and of clinical trials. The committee has the feeling that the director takes the risk to progressively loose contact with the research activity. Once a month a management committee, including the director, the five group leaders will meet to discuss scientific, budget, management and educational issues. The director of the NMR platform and the leader of the ENVA large animal platform will be invited to participate, but will not vote the decisions. In case of conflict, the director has the final decision. The communication among the group leaders and the director seems to be very good. Four times a year a statutory laboratory council comprising representatives of all personnel categories will meet. In particular authorship rights will be discussed to ascertain that students and senior researchers are given their due position on the publications they produce. The young group leaders that will compose the new unit rely on the director to manage the unit and deal with the budget. Funding is very comfortable and the space is sufficient for four young groups. Therefore, these groups are not limited in their
work and no conflicts were reported. Group leaders and those in charge of common facilities meet with the director every 4 months to discuss the general running of the unit.

- Of human resources:
Each group leader is in charge of the running of his/her staff. Each group is also in charge of a common technical facility. The technical staff involved in the platforms are integrated to the teams.

- Of the communication strategy:
Several recurrent events are organized to favour scientific exchange:
- weekly work-in-progress meetings where students and post docs present their ongoing projects
- journal club dedicated to students and post docs
- weekly clinic-genetic-morphological staff meeting open to all to favour exchange between the laboratory and the neuromuscular reference center
- National and international invited lectures
- 6 to 8 international workshops on selected topics are organized each year by the director.

These initiatives are much appreciated in the laboratory and highly contribute to the dynamics of the unit. They constitute an excellent training for students and post docs.

6 • Recommendations and advice

— Strong points:
This laboratory is composed of groups of excellent quality. The proximity of the clinical services, neuromuscular center and the biotherapy evaluation platform creates a environment unique in Europe.

— Weak points:
The physical separation of this laboratory with the Unit located at the 105 bvd de l'Hopital is regrettable, and although collaborations exist, it does not favour continuous exchange between clinical and fundamental research.

— Recommendations:
The two units evaluated by the committee work on very complementary topics, yet with different conceptions and goals. The ‘myology’ unit (unit 1) is rather oriented towards fundamental myology, whereas the ‘Therapy of Striated muscles disorders’ unit (unit 2) is rather oriented towards physiopathology and treatment of muscle diseases. However, the separation is not that sharp. For example, unit 1 has recruited a group, which was formerly part of unit 2, which is dedicated to the genetics, pathophysiology and treatment of early onset myopathies. Similarly, two groups of unit 1 will join unit 2 in 2009. Overall, the committee has unanimously felt that it would be a great benefit to have Unit 1 and 2 working together in the same building. However, the committee realized that in the near future it was not possible to achieve this goal, which should nevertheless remain a major issue in the future. The question of the reasons that made that the creation of two, rather than one unit engulfing these two, was also discussed. Obviously, in addition to the scientific rationale, the distribution of the groups between the two units has also been motivated by personal affinities or opportunities offered to the group leaders. It is also quite clear that the visions of the two directors are different and that, up to now, attempts to create a single laboratory failed. In addition, the necessity to have one instead of two units was not considered to be a priority, the important goal remaining to favour the geographic unification of the units, to facilitate contacts between researchers, postdocs, students... It is important to mention that active collaborations already exist between the groups of the two units, and that our recommendation is aimed at still reinforcing contacts between the groups.
Paris, le 2 juin 2008

Monsieur Jean-Jacques AUBERT
Directeur de la section des unités
AERES

N/Réf. : A1 – NL/SF-08-40
V/Réf. : AER_P06_053-UMR-UMRS-BG-V1.pdf

Objet : Transmission réponse DU

Monsieur le Directeur,

Je vous prie de trouver ci-joint, la réponse que le Directeur du laboratoire « Thérapie du muscle strié » a souhaité vous transmettre. Cette réponse est organisée en un ou deux fichiers attachés.

Je vous prie d’agréer, Monsieur le Directeur, l’expression de ma sincère considération.

Le président

Jean-Charles Pomerol

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Response to the report from the Visiting Committee, AERES, April 2008

The following response will be devoted to the discussion of some facts and some general comments, and will also give some supplementary information. The factual corrections have been detailed in a separate letter.

Discussion of some facts and some general comments

- **P5, 3rd para:** We agree that teams 1, 2, and 3 are large, whereas teams 4 and 5 are of standard size (14 and 7 members, respectively). We will assure that ambitious and successful researchers can develop towards complete independence if they wish to do so.
- **P6, team 3:** We recognize that with the recent integration of Helge Amthor, MD, PhD, into the group of Luis Garcia the work on myostatin might yet appear to be at a lower standard than the exon skipping work, even if a 1st author paper by H. Amthor was published in PNAS in 2007. We would like to add that currently another 1st author paper by H. Amthor is being submitted to a top ranking journal on this topic.
- **P7, Team 5:** We fully agree that the existing and fruitful collaboration between team 5 and teams 1-4 should ideally be embedded into a formal collaboration between the two universities, UPMC and UKE Hamburg, and we propose to develop structural connections to serve this purpose.
- **P7, re: quality of the management:** The Committee has commented critically that the director might be in danger to progressively lose contact with the research activity. In theory this risk might exist. In practical terms the director is actively involved in research projects of teams 1 and 3. He is furthermore actively involved in structuring worldwide clinical trials (member of the Steering Committee of the PTC 124 trial for Duchenne MD, PI of the planned SANTHERA omigapil trial for collagen VI-deficient MD). To structure these key trials reflects a prime interest of this research unit and should, we think, be regarded as a genuine research activity. He has a continuous flow of publications, and his papers have been cited >1200 times.
• P8, recommendations: We agree that the physical separation of the proposed unit at the 2 sites, 105 bvd de l'Hôpital and the Babinski building, is regrettable and should be overcome. However, we would like to emphasize that we also follow avenues of fundamental research within our unit in spite of the obvious orientation towards therapeutic goals in the short, medium and long term.

Supplementary Information

We would like to inform the Committee that since the date of the visit Vincent Mouly (team 2) and Luis Garcia (team 3) have successfully passed the competition for DR2 CNRS, and have been classified as second and first, respectively, by their commissions.

In addition, the two European FP 7 projects NMD-Chip and MYOAGE have received approval from the EU Commission, and contracts are being negotiated.

On behalf of the unit ‘Therapy of striated muscle disorders’

[Signature]

Thomas Voit