Génétique médicale et génomique fonctionnelle

Rapport Hcéres

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

Section des Unités de recherche

AERES report on the research unit

Génétique Médicale et Génomique Fonctionnelle

From the

Université d'Aix-Marseille 2

INSERM

February 2011

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Le Président de l'AERES

Didier Houssin

Section des unités de recherche

Le Directeur

Pierre Glorieux

February 2011

Research Unit

Name of the research unit : Génétique Médicale et Génomique Fonctionnelle

Requested label: UMR_S Inserm

N° in the case of renewal: UMR S_910

Name of the director: Mr Nicolas LEVY

Members of the review committee

Committee chairman

Mr Michel GOOSSENS, University of Paris-Est-Créteil, Créteil, France

Other committee members

Mr David ATLAN, Phenosystems, Brussels, Belgium

Mr Pascal MAIRE, Université Paris Descartes, Paris, France

Ms Fiona FRANCIS, Université Pierre et Marie Curie, Paris, France

Mr Romain GHERARDI, Université Paris-Est-Créteil, Créteil, France (Inserm)

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Observers

AERES scientific advisor

Mr Pierre LEGRAIN

University, School and Research Organization representatives

Mr Pierre CHIAPPETTA, Université de la Méditerranée

Ms Chantal LASSERRE, Inserm

Report

1 • Introduction

- Date and execution of the visit:

The visit took place in Hôpital La Timone, Marseille, on Thursday and Friday, February 3 and 4, 2011. After the committee briefly met in private, and following a brief introduction by the AERES delegate, the Unit director made a general presentation of the unit, its history, its research interests and the past and present scientific activities. The 9 team-leaders then presented their projects. After meeting with the institutional representatives, the committee split into three subgroups to meet with PhD students, engineers and technicians and researchers. The committee also had a half-hour discussion with the Unit director. A closed deliberation of the committee took place at the end of each day of the visit.

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

The unit that applies for re-creation, UMR_S910, is at present part of the Institut Fédératif de Recherche (IFR) located on Campus Timone, which federates 3 INSERM UMR (608, 626, 910), an INRA unit (1260) and a CNRS UMR (6612), along with 10 university hospital (AP-HM) clinical research centres or laboratories. The IFR manages several technological platforms, in particular suited to genomic medicine and research. UMR_S910, presently composed of 6 teams (Mental retardation and cortical malformations, Neuromuscular disorders and laminopathies, Epilepsies, Functional genomics, behaviour and pathologies, molecular bases of spermatogenesis), will be restructured into 9 novel teams through reshuffling and adhesion of new research groups. In the new organisation, the team led by the director, who is now centring his research activities on “Nuclear matrix and diseases”, will recompose by absorption of the former spermatogenesis team, which is orienting its interest on “nuclear matrix and spermatogenesis”. The previous themes “muscular dystrophies” and “Charcot-Marie-Tooth diseases” are taken over by new teams 3 and 5, respectively, team 5 being linked to an International Associated Laboratory from Lebanon. If some previous members are leaving the unit, three newcomers will bring novel but complementary expertise on “Epigenetics and chromatin regulation”, “Genetics and development of cardiovascular disorders” and “Axonal growth and neurodevelopment diseases”. A group specialized in “Genetics and bioinformatics” plans to move from Montpellier to join the new unit in a near future. As the IFR will be discontinued, the genomic platform will be integrated into and managed by the proposed unit; the present IFR director will join it, creating and leading a team working on “Human embryonic stem cells and iPS”. Overall, this re-organisation brings coherence and opportunities for interactions between the various teams that share molecular biology and genomic technologies, and that tackle identical or close biological and pathophysiological questions, making use of complementary approaches.

- Management team

Nicolas Levy manages the unit, with a management board composed of all team leaders, the director, the administrative assistant/secretary, two representatives ITA/IATOS, and delegates from the hospital-university staff and from the students.

- Staff members (on the basis of the application file submitted to the AERES)

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	15	20
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	9	11
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	11	16
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	15	22
N5: Number engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	4	9
N6: Number of Ph.D. students (Form 2.7 of the application file)	17	25
N7: Number of staff members with a HDR or a similar grade	19	28

N.B: includes all staff members from Research teams and Platforms

2 • Overall appreciation on the research unit

- Summary

The unit under renewal is composed of 9 teams: team 1, "Neurogenetics" (Laurent Villard), team 2 "Nuclear envelope and diseases (Nicolas Levy), team 3 "Translational myology (Marc Bertoli and Martin Krahn), team 4 "Genetics and development of cardiovascular disorders" (Stéphane Zaffran), Team 5, "Genetics and Pathophysiology of autosomal recessive neurological disorders" (Valérie Delague and André Mergabane), team 6 "Epigenetics and chromatin regulation" (Frédérique Magdinier), team 7 "Axonal growth and neurodevelopmental diseases" (Fanny Mann), team 8 "Human embryonic stem cells and iPS" (Bernard Binetruy) and team 9 "Genetics and bioinformatics" (Christophe Béroud).

The teams share approaches and technology taking advantage of core facilities (cell biology, western blots, CGH-CHIPS) in a multidisciplinary setting (clinicians, biologists, bio-informatics specialists). They collaborate and/or interact to develop a high level translational research programme that exploits well phenotyped patient cohorts in the domains of neurogenetics (cortical malformations, epilepsies, « MeCP2-pathies »), axonal neuropathies (various CMTs, muscle disorders (DMD, LGMDs, FSHD,…), heart defects (del22q11,…), methylation disorders (PWS/AS), spermatogenesis defects (male infertility), NE associated disorders (laminopathies, aging disorders), chromosomal abnormalities / contiguous gene syndromes.

- Strengths and opportunities

- The excellent integration into the local medical community, and the availability of large cohorts of patients affected by monogenic disorders for which the clinicians of the Department of Medical Genetics and Cell Biology (17/24 HU/H belong to the various scientific teams of the unit) are renowned experts. This asset has been a key factor to attract the new teams. Some of the members participate or coordinate relevant Reference Centres for Rare Diseases (Developmental, Neuromuscular, and Metabolic diseases)

- The many partnerships and links through international networks and as members (or coordinator) of European projects: European network on Rett syndrome, DisChrom (EU Marie Curie), NMD-Chip, Euro-Laminopathies, conferring a recognized international visibility.

- The involvement in several preclinical or clinical/therapeutic trials (Progeria, Rett Syndrome, Duchenne muscular dystrophy), and the ability to obtain patents (7) and licences (2). The unit does very well in exploitation of its research results. Creation of a start-up company (Prenyl Bio).

- The ability to collect appreciable grants and financial support (1.14 to 1.18 M€ for 2008-2010)

- The top-notch expertise in genetics and development (congenital heart defects, axonal growth, neurodevelopment disorders, congenital dermopathy and progeria) and in epigenetic and chromatin regulation, along with original in vivo and ex vivo experimental models that are imported by the new comers.

- The charisma, energy and enthusiasm of the unit director, who, in addition to his local responsibilities, holds a key position in the animation/organisation of the French rare diseases programme at the national level.

- The well-organized continuum between research, molecular diagnostic and the clinic: the research is mainly translational.

- Weaknesses and threats

- For some projects there is a need to increase the critical mass, and some teams should be careful to avoid over diversification of projects.

- The difficulty, for some projects, to design and successfully carry out relevant functional investigations of the identified mutations.

- The difficulty to maintain, in the long term, the cohesion of the whole unit, important to achieve the common goal.

- Recommendations

The director will have the difficult but important task to maintain the cohesion of the whole unit and its adhesion to the common, global project. He should push for cross-fertilization and interactions between the old and new teams, in order to improve the quality of the research, taking advantage of the novel and dedicated expertise introduced. Management efforts and attention are required to best exploit this added value.

- Production results

A1: Number of permanent researchers with teaching duties (recorded in N1) who are active in research	20
A2: Number of permanent researchers without teaching duties (recorded in N2) who are active in research	11
A3: Ratio of members who are active in research among staff members [(A1 + A2)/(N1 + N2)]	1
A4: Number of HDR granted during the past 4 years	3
A5: Number of PhD granted during the past 4 years	14

3 • Specific comments

- Appreciation on the results

  – The relevance and the originality of the research, the quality and the impact of the result

The research programme and its results best exemplify what is called « translational research ». Starting from patients (the clinicians, members of the unit, and managing three reference centres for rare diseases, attract large cohorts of affected families), the teams seek to identify the defects, to unravel the pathophysiology, and to develop diagnostic assays and relevant molecular, pharmacological or cellular therapies. The quality is high overall, as shown by the scientific production (see below) and the impact is strong as shown by the exploitation of research accomplished (patents and licences, start-up company), and the therapeutic trials in progress.

  – The quality and the number of the publications, scientific communications, thesis and other outputs

During the past 4 years, the unit has contributed important results, publishing more than 330 articles, among them 184 published as 1st or last author and directly related to the unit projects, in good impact factor journals (see specific team reports), and filing 7 patents and 2 licences. There were 82 invited conferences in international meetings.

  – The quality and the stability of partnerships

There is a remarkable ability of the unit to engage in partnerships at the national and international level. The following partnerships and networks are:

- European network on Rett syndrome, with 14 partners (2008-2011), coordinated by Team 1 leader (155 000 €)

- DisChrom, EU Marie-Curie Training Network (2010-2014), 4 countries in which team 1 is partner (210.000 €)

- NMD-Chip, with 13 partners (2008-2011), coordinated by Team 2 leader (3.000.000 €)

- Euro-laminopathies, with 15 partners (2006-2009) (200 000 €)

- RADICO, a Cohorts project (Grand Emprunt) in which the University is partner through its Med Genetics department and the UMR_S 910.

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

The unit has a very good national and European visibility. Several team leaders are renowned in their field of research and were awarded scientific prizes (see individual teams), and are regularly invited to international conferences (82 during the last 4 years)

Four novel teams joined or will join soon the unit, headed by high level scientists who have been attracted by the excellent scientific environment, the availability of patient cohorts, the good financing of the unit and the key positions held by the director at the national level in the “Maladies Rares” domain.

In part due to their engagement in research on neuromuscular disorders and links with AFM and other Charities, but also because of their other talents, the various groups have been so far very successful in obtaining research grants (1 185 364 Euros collected in 2010, AFM funding for 2010-2014 is 3,6M€).

The unit members are very active in international and national scientific networks (See above and in team reports for details on partnerships and networks).

The unit has filed 7 patents, 2 licences, and one start-up company was created (Prenyl Bio SAS).

- Appreciation on the management and life of the research unit

UMR_S910 and 608 have been selected at the national level to experiment a new form of administrative management with the university (Délégation Globale de Gestion or DGG). Major delegations are given by the director to team leaders and researchers, with a management board which is in charge of anticipating the purchase of equipment, discussing recruitments, and helping the career progression of PhD, Post-docs, and ITA.

Well planned organisation with internal seminars (research and clinical), Journal Club, English spoken team meetings.

Teaching: most researchers are involved in teaching activities (medical graduate programmes, masters 1 and 2), and some teach in summer schools.

Structuring of research: as renewal of the IFR will not be applied for, the unit is taking over the management of several core facilities such as the Genomic-transcriptomic platform, the animal facilities, and the cell imaging facility applied to exploration of small animal models. Funding has been obtained from AFM to implement a deep sequencing core facility, and there are plans to develop on site, inside the unit (team 8) a laboratory dedicated to creating and using iPS cells.

- Appreciation on the scientific strategy and the project

This unique organisation of the unit, which widely facilitates cross-interaction and exchanges between clinicians, clinical molecular geneticists, and basic researchers, is the backbone of the high level translational research effort engaged from bedside to pathophysiology, novel diagnostics and therapies. The very good funding capabilities, the added-value contributed by the newcomers (neuro and cardio-development, epigenetics, bio-informatics), overall give credit to the whole scientific project, which is certainly feasible with expected successes in the next four years.

The research Unit UMR_S 910 is funded annually by a recurrent grant from INSERM (190 K€ HT) and the university (56 K€ HT): total: 246 K€ HT. Besides, private (foundations, patient's associations) and public contracts (ANR, EU) are requested and obtained each year to fund specific research programs. The allocations of public resources are split in two parts:

- A definite part (around 60 %) is put aside for the common expenses of the unit (common services, platforms, running, operation, administration, etc.)

- The rest is specifically allocated to individual research teams in proportion to the number of full-time researchers.

The teams joining the unit during the four-year contract have access to the platforms and common services and benefit from the common funding and they enjoy the benefit and advantages provided by a common office management.

None of the resources obtained from specific research grants/programmes is formally used for the common services and platforms. However, the part, from each contract, which is devoted to the purchase of equipment benefits the whole unit, every team having access to all the equipment present in the research unit.

There are several projects, in particular on aging disorders, axonal growth and neurodevelopmental disorders, genetics of cardiac defects and epigenetics that are, in very competitive domains, original, ambitious and at the forefront of their research domain (see relevant team reports).

4 • Appreciation team by team

Team 1 : Neurogenetics

Team Leader : Laurent VILLARD

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	2	2
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	3	3
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	3	3
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	2	4
N7: Number of staff members with a HDR or a similar grade	5	5

- Appreciation on the results

This is interesting and relevant research with a translational impact. For example, team 1 has exploited findings concerning breathing regulation to prolong life in a mouse model of Rett syndrome (patent application, and foundation for a phase IIa clinical trial). In a second project, a clinician from the team has organised a national network to study rare cortical malformations. Data from this panel of patients contributes to many studies. In-house two genes have been identified (Hum. Mutat /J. Med. Genet). In a third project a cohort of patients has been collected for a severe form of neonatal epilepsy, one new gene has been identified.

26 publications arise directly from group activities (equivalence of 12.75 full-time personnel). There are also 50 additional publications including a certain number with a single member of the team as co-author in a non-principal position. Team 1 leader has 11 last author publications since 2006, (highest impact journal is Hum Mutat). The team has one existing patent (2005), with a positive opinion from the EMA for designation of an orphan drug and the license sold to a pharmaceutical company. One provisional patent application has been filed. This team had 17 invited conferences. 4 PhD students defended their theses (each in 3 years), and 1 HDR defended.

The quality and the stability of partnerships is very good. In an addition to national networks, the team is implicated in two European projects. 10 collaborating groups are named (7 non-French). The team has an industrial partner.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

No awards mentioned. The team members had 7 oral communications in congresses in Europe and 3 further oral presentations in European Rett Syndrome network meetings in Italy.

The team is comprised of 1 full time researcher, 1 post-doc, 3 PhD students, 3 affiliated clinicians, 1 university professor and 4 tech/engineers, very few if any from abroad.

The ability to raise funds and to participate to scientific networks and industrial collaboration are excellent. The team has funding from national and international sources and is present in 2 European networks (2 PHRC, 2 GIS

Institut des Maladies Rares, 3 ANR grants, Association Française du Syndrome de Rett, 2 European grants (ERA NET E-RARE and ITN network), Rett syndrome research foundation, Fondation Jérôme Lejeune, Fondation Française pour la Recherche sur l'Epilepsie). It collaborates with Targeon Pharma.

This team has created a national network and is involved in two European networks and has 7 non-French collaborators.

The transfer of results to industry is excellent with one patent (2005) for which positive opinion from EMA for designation of orphan drug was obtained, and a license sold to pharmaceutical company, as a foundation for a phase IIa clinical trial. One provisional patent application is being filed. The RettCure project is in collaboration with Targeon Pharma.

- Appreciation on the scientific strategy and the project

The projects described are solid and feasible, the questions are good, funding has been obtained. E.g. Gene therapy for Rett Syndrome, genetic projects for cortical malformations and neonatal epilepsy, transgenic mouse mutant studies for genes of interest. The team seems to have adequate funding. The exploitation of research results is worth highlighting, as is the potential for the identification of new genes for neurodevelopmental disorders (results could be cutting edge if backed up by pertinent functional studies).

- Conclusion :

  - Summary

This group is strong clinically and genetically and in translational work. Basic functional studies are also carried out (transgenic mutant mice, anatomy and behavioural studies). There is a potential to identify new genes in cortical malformations. The group publishes numerous papers, is involved in many collaborations and has created good networks. The group is well funded.

  - Strengths and opportunities

Good exploitation of results (bench to bedside) to treat symptoms of RETT in collaboration with a pharmaceutical company. Good collections of patients with rare disorders, shared with the scientific community. State-of-the art genetic screening applied to such panels.

  - Weaknesses and threats

The challenge of setting up pertinent functional studies to understand the role of the novel genes identified.

  - Recommendations

Further pertinent physiopathology strategies may be appropriate to help validate and characterise new genes identified in the future.

Team 2 : Nuclear Envelope and Diseases

Team Leader : Nicolas LEVY

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	8	5
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	6	4
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	4	3
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	3	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	7	4
N7: Number of staff members with a HDR or a similar grade	9	6

- Appreciation on the results

Team 2 has been derived from the original research team lead by Prof. Nicolas Levy, which worked on 1) Laminopathies, 2) Muscular dystrophies, 3) Charcot-Marie Tooth diseases. Three groups (Teams 2, 3, 5) emerged from the original team in 2009.

Team 2 is now engaged in the study of Nuclear envelope and disease and it is divided into 2 sub-groups: A) Molecular genetics of Spermatogenesis and the nuclear lamina: contribution to male infertility and B) Laminopathies: nuclear envelope and associated disorders. Group 2A is engaged in the study of the composition of the nuclear lamina during spermatogenesis, with a focus on A and B type lamins, LBR and their partner proteins, under normal and pathological conditions. The group leader has a long-lasting expertise (since 1996) in the study of human spermatogenesis and 15 publications in the field. Group 2B is engaged in the study of laminopathies caused by LMNA or ZMPSTE24 mutations, namely premature ageing diseases such as Hutchinson-Gilford Progeria syndrome (HGPS) and developmental diseases such as Restrictive Dermopathy, a lethal neonatal laminopathy. The group remains the best qualified in Europe for the study of these disorders since they discovered mutations in the LMNA gene causing Progeria (DeSandre-Giovannoli et al., Science 2003) and ZMPSTE24 or LMNA mutations causing Restrictive Dermopathy (Navarro et al., Human Mol Genet., 2004 and 2005). In recent years, the group has implemented a therapeutic strategy in collaboration with the Spanish group of Dr. Carlos Lopez-Otin, based on the use of statins and biphosphonates (Varela et al., Nature Med. 2008). A clinical trial has been approved and it has started in Marseille at The Hospital La Timone, based on the use of the same drugs. The quality and the impact of the results obtained in the field of progeria and restrictive dermopathy studies are excellent.

A limited number of high impact publications (Nature Med.; J Med Genet. ; Stroke. ; Hum Mol Genet.) shows the high level of the results and a high number of medium impact publications (2 in Am J Med Genet ; J Mol Med ; Mech Ageing Dev. ; Aging Cell) shows the continuity of the research activity in the field of laminopathies. The number of invited lectures on laminopathy research is 49 in the period 2006-2010.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team participated to 49 international conferences and symposia, as invited speakers. Team members were awarded 4 national prizes.

9 students (MD or PhD students) have been included in the Team. Most students are from France or French-speaking countries. A MD from Italy has also been included.

14 grants were obtained by the team in the period 2006-2010 with a total of more than 1M € (funded by AFM, EU-FP7 NMD-Chip and BIO-NMD, ANR). The amount of funding and relevance of funding organizations (EU, AFM) is excellent.

3 patents have been obtained (in 2007, 2008 and 2009 : patents for the use of combined medicines obtained by statins and biphosphonate in human therapy and in cosmetic preparations).

Several national and international collaborations (Oviedo, Spain ; Rome, Italy) and the participation to EU-funded projects FP6 Euro-laminopathies, FP7-BIO-NMD and Treat-NMD constitutes a strong research asset.

- Appreciation on the scientific strategy and the project

The projects include: 1) characterization of 2 new mouse models for progeria – excellent – feasible in 4 years, 2) identification of morpholinos to avoid aberrant splicing in progeria – very good – feasible, 3) identification of new treatments for progeria children (statin + alendronate + growth hormone axis stimulating drugs), excellent, feasible 4) definition of the nuclear lamina composition and its role in spermatogenesis, good, feasible.

Resources have been obtained from several national and international funding organizations. Several common technical platforms have been established (genomics and transcriptomics, animal facilities, cell cultures, imaging, flow cytometry): there is a good optimization of resources.

The proposed projects, mostly those aimed at HGPS patients' cure are cutting edge projects. Some projects, including the one aimed at analysing the nuclear envelope during spermiogenesis, are novel and may lead to important translational results.

- Conclusion :

  - Summary

Overall, Team 2 has a high potential to provide new translational results and relevant advances in the field of nuclear-envelope linked human diseases, a group of more than 15 inherited or acquired diseases, among which are progeroid syndromes.

Team 2 includes two main subgroups: group A – the nuclear lamina during spermiogenesis and its contribution to male infertility - and group B – nuclear envelope and disease. Group B includes two subgroups: "Translational Research in Prelamin Associated Diseases" and "From rare genetic diseases to frequent and acquired disorders". The latter two subgroups seek to devise a therapy for HGPS and Restrictive Dermopathy, and to identify lamin-linked molecular mechanisms of acquired lipodystrophy in HIV infected patients undergoing highly active anti-retroviral treatment, respectively. Team 2 has already obtained important results, the clinical team is carrying out a clinical trial in 12 HGPS patients using a combined treatment with statins and biphosphonates and 3 patents for these and other drugs and two licences have been obtained. The Team leader published 25 papers related to the specific topic of Team 2 and has been invited to 49 national and international conferences. The team also obtained 3 patents and created 1 start-up company in the period 2006-2010.

The staff involves clinicians, biochemists and post-docs and students (5 PhD students, 5 thesis defended). While the leadership is excellent and appears to coordinate properly the group, the number of scientists involved in basic research could be increased and the researchers could be assigned to different subgroups for the study of laminopathies. One researcher has been recently recruited. Overall, the very high potential of the group will provide new important advances in the field of nuclear envelope-linked human diseases.

  - Strengths and opportunities

Excellent quality of the proposed projects and availability of experimental models (mouse Lmna-KI G609G, other Lmna mouse models, HGPS fibroblasts, other laminopathic cells). Excellent link between clinicians and researchers, favouring exchange of data and samples, and of knowledge. Ongoing clinical trial for HGPS patients (alendronate + statin treatment) and availability of new protocols to be tested (including somatotroph axis stimulating drugs). The team leader has much talent for fund raising. Good interplay with the University and attraction of PhD students.

– Weaknesses and threats

Low number of full-time researchers may be a handicap.

– Recommendations

Increase the number of full-time researchers (permanent position or post-docs) and technicians involved. Aim at increasing the number of high impact factor papers.

Team 3 : Translational Myology

Team leaders : Marc BARTOLI and Martin KRAHN

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	×	3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	×	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	×	4
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	×	1
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	×	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	×	2
N7: Number of staff members with a HDR or a similar grade	×	4

- Appreciation on the results

This is a novel team of small size issued from the division of Nicolas Levy previous team into 3 parts. The team is co-directed by a young CR1 CNRS (Marc Bartoli) and a young MCU-PH geneticist (Martin Krahn). It is too early to comment on stability of this partnership. An excellent point is that expert MDs handling the large cohorts of neuromuscular diseases investigated by the group belong to the team.

This is most relevant translational research mainly based on two impressive cohorts of rare myopathic diseases: dysferlinopathies and facioscapulohumeral muscular dystrophy (FSHD). For dysferlinopathies, the group has set up outstanding diagnostic tools including the Universal Mutation Database for dysferlin and high throughput mutational screening (FP7 projects NMD-chip and Bio-NMD). Moreover, they successfully developed innovative preclinical genotherapeutic approaches, including rAAV-minidysferlin transfer in a mouse model of dysferlinopathy (Science Translational Medicine 2010) and dysferlin exon 32 skipping in cell culture (Hum Mutat 2010). For FSHD, the group had focused on pathophysiology of the disease, which remains very poorly understood, by developing a promising molecular combing approach (in collaboration with "Genomic vision", Paris) and high throughput analyses.

Other programmes are at less advanced stages of development. For example, modulation of eosinophils is proposed as a possible treatment of calpainopathy. This programme is based on original histopathologic observations published by team 1 but no preliminary result supporting proof of concept was shown.

Publications are not abundant but include excellent (Science Translational Medicine) or very good (several Hum Mutat) papers for dysferlinopathies. It is less impressive for other projects if one excludes 1 Ann Neurol, and an

important collaborative paper (submitted). Other papers in Clin Genet (2), Eur Hum Genet (1), Genet Test Mol Biomarkers (2), Neuromusc Disord (1). Researchers of the team 3 have filed 1 patent on dysferlin and FSHD, directly related to their results.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

- Scientific links of this team are excellent, as exemplified by the on going collaboration with a renowned genethon team working on dysferlin (Evry). Gene therapies are designed in close collaboration with another renowned group working on exon skipping strategies (UPMC, Paris).

- The team is young and it is therefore small. However, two post-doc positions have been recently obtained by the team, which will significantly strenghthen its research potential. Regarding, the impressive bulk of PhD students attracted by the unit each year, there is no doubt that some will join team 3.

- Nicolas Levy, former director of the team, has demonstrated impressive capacity to raise funds from both national and european sources

- Dysferlin and FSHD have been important factors of visibility of the unit from 2006 to 2010 (12 invited conferences on these topics)

- Appreciation on the scientific strategy and the project

Several translational programmes are ongoing at both the diagnostic (dysferlin, neuromuscular diseases in general), physiopathologic (FSHD) and therapeutic (dysferlin, calpain) levels. Diagnostics are conducted on large and almost unique cohorts of patients (dysferlin, calpain) using hi-tech approaches. Physiopathology is investigated using novel approaches such as molecular combing. Confirmation that a first mouse model of FSHD has been defined in collaboration with Luminy will probably influence future physiopathologic investigations on the disease.Therapeutic attempts are at various stages of development (research of proof of concept, feasability on cell culture, preclinical animal study) and will last many years from now. Many aspects of these projects are at the cutting edge in the field (rAAV-minidystrophin, dysferlin exon skipping, molecular combing, etc).

- Conclusion :

This is a novel team of small size issued from division of Nicolas Levy previous team into 3 parts. Recent and prelimary results on dysferlinopathy and FSHD are most promising.

– Strengths and opportunities

- Important cohorts of rare diseases governed by MDs involved in the team

- Hi-tech molecular genetics

- Good environment and scientific connections

- Important funding

– Weaknesses and threats

- Young bicephalous group with little experience in management

- Scientific autonomy not yet established (most topics set up by Nicolas Levy)

- Heterogeneous publication record

- Unsufficient manpower

– Recommendations

- Engage active recruitment of post-doc and PhD students

- Efforts to reach a generally higher level of publication are necessary

- Codify respective implication of the two leaders and the relationships with Nicolas Levy

- Define policy of funding allocation

Team 4 : Genetics and Development on Cardiovascular Disorders

Team Leader : Stéphane ZAFFRAN

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	3
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	2	2
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	✕	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	✕	1
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	1	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	1	1
N7: Number of staff members with a HDR or a similar grade	1	4

- Appreciation on the results

The team is involved is deciphering the molecular genetic basis of congenital heart diseases (CHD) in man. It appears that most of the CHD result from embryonic heart malformations. Two main aspects are developed. The first concerns the identification of the causative genetic basis of the disease in patients with CHD. For this aspect the group leader has developed many fruitful national (hospitals La Timone, and Necker, Paris), and international (University of Utah, University of Philadelphia) collaborations (transatlantic network) to obtain a cohort of patients. Using whole genome sequencing mutant genes will be identified responsible for the different forms of the pathology. The second aspect stems from observations the team made on the role of retinoic acid during embryogenesis. For that purpose several complementary mouse models have been developed and studied, that led to major results. Results already published (2 PNAS, Development, Circulation research…) establish that retinoic acid signalling during embryogenesis is required to instruct cardiac progenitors of the second heart field to adopt a cardiac fate. Some significant targets of retinoic acid have been identified belonging to the Hox genes family. The quality of the results obtained is of major interest both for our understanding of heart organogenesis during development, and also for understanding human pathogenesis.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

Invitations of the team leader for several national and international communications indicate that the work performed is recognized and has reached international standards. Dr Zaffran has built a new team in N.Levy's Unit, and has already recruited talented researchers and PUPH with several complementary expertises. These expertises will allow the development of the planned projects in excellent conditions. For example, the recruitment of an embryologist specializing in neural crest cells will allow the understanding of the involvement and the dialogue of these cells during second heart field development. The presence of a PUPH has allowed the creation of an excellent networking with the clinicians, and reinforces the translational research perspective. The team has obtained national grants (ANR, AFM) to support these projects. The group is involved in an international grant application (through a transatlantic network), and has established robust national and international collaborations.

- Appreciation on the scientific strategy and the project

The projects presented should provide information on the major genetic determinants operating during the first steps of cardiac cell determination during embryogenesis, the signalling pathways orchestrating engagement of pluripotent cells in the cardiac lineages, and the different cell populations involved (laleral mesoderm cells and neural crest cells). Furthermore, analysis of the expression patterns of the CHD candidate genes identified in human patients, in mouse embryos will allow a characterization of their functions in mammals and explain their causes and the embryonic history of human heart malformations.

- Conclusion :

  – Summary

The results already obtained by the different members of the team on heart development and human CHD are very significant. Complementary expertise of the team members, running collaborations, and the grants obtained will allow the ambitious projects proposed to be pursued under the best conditions.

  – Strengths and opportunities

- Complementary expertise of the team members in heart development, mouse KO animals, chick embryology, human heart diseases. The team is composed of talented clinicians, embryologists, and biologists.

- Cohort of patients with CHD.

- Access to new generation DNA sequencing.

  – Weaknesses and threats

Absence of post doc.

  – Recommendations

Keep going.

Team 5 : Genetics and Pathophysiology of Autosomal recessive Neurological Disorders

Team leader : Valérie DELAGUE

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	×	4
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	×	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	×	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	×	2
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	×	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	×	3
N7: Number of staff members with a HDR or a similar grade	×	4

- Appreciation on the results

This novel team emerged from the gathering of a group (directed by Valérie Delague) coming from the previous Team 2 (directed by Nicolas Lévy) and members of the unit directed in Lebanon by Mr André Mégarbane, which has obtained this year the label of Inserm International Associated Lab. The added-value provided by this gathering appears interesting, considering i) the long lasting close collaboration between both groups (>10 years, 40 common publications), ii) the convergence of research interests, iii) the complementarities of expertise developed in both groups. Since 2006, the active collaboration between Marseille and Beirut led to the identification of two novel disease-associated loci (dystonia DYT17 and leukodystrophy with oligodontia) and three novel genes (Charcot-Marie-Tooth type 4H, odonto-onycho-dermal dysplasia and CAMOS, a syndromic non progressive congenital ataxia).

The research on CMT2B1 associated with the LMNA mutation R298C is aimed at the identification of signalling partners of lamin A/C, whose binding could be affected by the homozygous mutation, which could in turn elicit deleterious effects. This approach is timely and promising. The research in this field resulted into two publications (Ann Hum Genet. and Neuromolecular Med.). The study of other CMT forms (CMT4H) performed by the Team 5 will help understanding the disease mechanisms.

As a novel team, the evaluation of previous results would normally be non applicable. However, the pre-existing close collaboration permits to have good feelings about the common past activity. 40 publications are referenced in Pubmed, with at least the name of the two team leaders (V Delague and A Mégarbane), including 13 since 2006. The highest impact journal is Am J Hum Genet (two common papers with one of the leaders being first or last author). The last gene (CAMOS) was published in Eur J Hum Genet, thus the authors could perhaps have been more ambitious in publishing in higher impact journals.

The team has very good national and international stable collaborations and partnerships, mainly in the Mediterranean area (Lebanon mainly, but also Tunisia, Algeria, Italy and Spain)

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team leader participates at international conferences (2 oral presentations; 10 printed communications including 2 as last author in the 58th ASHG annual meeting in 2008 – Philadelphia)

The team is attractive with currently 4 PhD students (including two foreigners, one from Lebanon) and 1 post-doc (from Lebanon) working in the team. The team also has 3 affiliated clinicians (2 PU-PH and 1 PH), and 2 tech/engineers.

Funding is very good with grants from national and international sources: Association Française contre les myopathies, RNG/INSERM (GIS-maladies rares), Agence Universitaire de la Francophonie and Avérroès program.

This team was created on the basis of the close pre-existing collaboration with the team in Lebanon.

- Appreciation on the scientific strategy and the project

The projects described are developed along two axes:

First, the team focuses on pathophysiological studies in the field of Charcot-Marie-Tooth disease, and more specifically on two forms for which the responsible genes have been previously identified in the Unit (LMNA and FGD4). The parallel development of cellular models and transgenic mutant mice is important to avoid major bottlenecks. The projects are relevant and feasible, even if functional studies (in cell models as well as in animal models) are certainly very difficult to do in laminopathies due to the low number of available samples from affected patients and the absence of biomarkers of the disease. The Team has constructed an animal model of CMT2B1 bearing the homozygous Lmna R298C mutation, which will provide important information. The study of LMNA promoter activity under normal and pathological conditions is novel and could provide unexpected pathophysiology data. The studies planned on CMT4H are more specifically devoted to decipher the relationships between axons and Schwann cells, and between abnormal endosomal processing, abnormal axonal transport and the consecutive occurrence of neurodegeneration in the peripheral nervous system. The questions posed are pertinent, funding has been obtained.

Second, in the collaboration with the international laboratory based in Lebanon there is a focus on the identification of novel gene defects causing autosomal recessive neurological disorders. Several consanguineous families with high genetic informative potential have already been identified and the project appears clearly relevant and feasible.

The exploitation of research results by this group is worth highlighting, as is the potential for the identification of new genes for autosomal recessive neurological conditions (results could be cutting edge if backed up by pertinent functional studies).

- Conclusion :

  – Summary

This novel team brings together two complementary groups associating good clinical, genetic and functional expertises. They have the potential to identify new genes in rare autosomal recessive disorders and to decipher molecular mechanisms involved in CMT2B1 and CMT4H. A strong collaboration between members of the team exists for many years. The group is well funded.

  – Strengths and opportunities

Availability of interesting cohorts of patients with rare neurological disorders occurring often in consanguineous families, through a non-formalized network. State-of-the art genetic screening applied to such panels, along with functional studies on the diseases identified could lead to important discoveries.

  – Weaknesses and threats

Although the high quality of previous research and publications of the collaborative work are evident, one could raise doubts concerning the clear strategy of the team independently form the associated international unit.

– Recommendations

- To identify clearly the leadership of the team in which some members (including the Head) of the Beirut Inserm International Associated Lab would be included.

- To highlight the pathophysiological studies of the team, which are specifically directed on former and future genes identified in collaboration with the international associated lab.

- To perform studies on the animal model of CMT2B1 (Lmna mutation), under stress or activity stimuli.

- To identify a Post-doctoral student to work on Lmna studies.

Team 6 : Epigenetics, Chromatin and Diseases

Team Leader : Frédérique MAGDINIER

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	✕	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	1	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	✕	0
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	✕	1
N6: Number of Ph.D. students (Form 2.7 of the application file)	3	4
N7: Number of staff members with a HDR or a similar grade	1	2

- Appreciation on the results

The team was created in July 2009 and the team leader has been working in Marseille on a full time basis since July 2010. This group is focused on chromatin research and its main goal is to better understand the deleterious role of the D4Z4 alteration on the subtelomeric region of chromosome 4, which is known to be linked to Facio-Scapulo Humeral Dystrophy. Importantly, the link between the altered chromosome 4 subtelomeric defect and structural proteins of the nuclear periphery such as lamins, has been determined. The originality and quality of the research is high. The team has produced during the 2009-2010 period high-level publications (Plos Genet 2010, J Biol Chem, 2010, Cell, 2010). The partnership with E. Gilson's unit in Nice provides the team with a fruitful exchange of expertise and knowledge in the field of research and in particular on telomere biology.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

Among 18 lectures given in France and abroad, the PI was invited to the National Center for Biological Sciences, Bangalore, India (2009) and Medical Research Council, Imperial College of Medicine (2009).

Grants have been obtained from ANR (Genopath programme) and associations (FSHD Global, FSH Society, AFM).

Although the team is quite small, it is very attractive, since good and well-defined starting points have been settled.

- Appreciation on the scientific strategy and the project

This project brings an added value to the research carried out by team 3 on the underlying mechanisms involved in FSHD. This move to epigenetic regulation of human subtelomeres and implications in diseases, which uses state-of-the art technologies, is in this context really innovative and forward-looking. It will likely result in significant contributions over the next four years.

- Conclusion :

– Summary

The expected input of this recently created team is well suited to the general strategy of the unit and provides a real added-value through the complementary expertise introduced, in particular in the field of chromatin and epigenetic research.

– Strengths and opportunities

The team leader has a very good and specialized expertise in the field of chromatin epigenetic studies. The tight collaboration and links with clinicians in the Hospital La Timone will provide relevant patient material, allowing validation of the experimental results in the proper human disease model.

– Weaknesses and threats

The team is quite small, although some students are also involved.

– Recommendations

It would be wise (1) to increase the critical mass by recruiting a couple of full time permanent researchers (2) to augment the number of international collaborations and (3) to strengthen the links with other researchers of the unit and its members working in the clinical genetics department, especially involved in human cytogenetics.

Team 7 : Axonal Growth and Neurodevelopmental Disorders

Team leader : Fanny MANN

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	X	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	X	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	X	0
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	X	0
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	X	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	X	2
N7: Number of staff members with a HDR or a similar grade	X	2

- Appreciation on the results

This is a young team, from the IBDML, Marseille, expecting to join the unit in Spring 2011. This group has a previous track record of excellent and original work eg a publication on the role of axon guidance receptors (Neuron 2007) or the interplay between actors of neuronal and vascular development (Neuron 2010). This is relevant and original work leading to high impact publications. Also 1 patent has been filed for a molecule designed to block Sema 3E action in tumours. In total, the team has 6 main publications, 3 with an impact factor greater than 12 and 3 collaborative publications. 1 patent has been filed, I thesis defended.

They were invited at 12 conferences, with three international conference and 3 national communications.

The team has many collaborations nationally and internationally, with a number leading to joint publications. It also has joint studies with industry (Netris Pharma).

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

- F. Mann was awarded the Bronze medal of CNRS in 2010.

- This young group (mainly French) has already attracted high-level students.

- This group has been obtaining competitive funding since 2006 (ANRJC, FRC, INCa, FBF, NRJ Foundation, AFM, FRC, ARC, FRC, ANR). One PhD student is funded from an Industrial fellowship.

- This group is involved in 12 international collaborations, of which 6 have already produced a joint publication. The group also has 6 national collaborations of which two have produced a joint publication.

- This group has filed one patent in 2010.

- Appreciation on the scientific strategy and the project

This group will set up time-lapse confocal imaging of living axons in brain slices to study forebrain commissure development. Such an assay will be used to study molecular mechanisms downstream of receptors, including the use of multicompartment cell-culture chambers to isolate axons from cell bodies. Key molecules will be studied in expression studies in human foetal brain and proposed as candidates for forebrain commissure ageneses. These studies are relevant and feasible and constitute an excellent project.

The projects are original (few labs are studying axon motility dynamically in brain slices, and little is known about downstream signalling pathways). Also the retrograde transport of molecules regulating transcription from the growth cone to the nucleus seems to be an interesting project with potential.

- Conclusion :

  - Summary

This is a young talented group with an excellent publication record, a filed patent and original projects.

  - Strengths and opportunities

The projects have potential, use state-of-the-art technologies and are linked to multiple pathologies, including cancer and neurodevelopmental disorders

  - Weaknesses and threats

The group should increase its size by recruiting new people.

  - Recommendations

In its new environment, this team should continue to remain focused and to generate landmark data suitable for high quality journals.

Team 8 : Human Embryonic Stem Cells and iPS–M.

Team leader : Bernard BINETRUY

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	×	0
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	×	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	×	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	×	1
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	×	0
N6: Number of Ph.D. students (Form 2.7 of the application file)	×	3
N7: Number of staff members with a HDR or a similar grade	×	1

- Appreciation on the results

The team is engaged in three overlapping programmes dealing with embryonic ES cells and induced pluripotent stem cells (iPS).

Concerning ES cells, the team has shown :

-The implication of p38MAPK in ES-derived mesoderm cell fate. Blockade of the pathway impairs mesoderm and cardiomyocyte formation, favouring neural induction (articles in Stem Cells, Stem Cells & Development).

-The role of FoxO transcription factors in the activation of dopaminergic neurons in embryoid bodies. Otx2 known to be a FoxO3 target in neurons is required to specify neuron subtype. Otx2 expression is induced in modified ES cells expressing an inducible form of FoxO3 (collaboration with a US laboratory).

The team also plays an important supportive function in the unit by establishing for other teams both murine and human (in collaboration) iPS cells. For example, iPS cells derived from FSHD (team 3 and 6) and progeria (team 2) patients, and from the relevant mouse models (e.g. the Zmpste24 KO mouse that recapitulates progeria), offer the possibility to establish new experimental tools and open potential new avenues for cell therapies for these pathologies.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team leader is presently Director of the IFR IPHM, and member of the INSERM U626. He will quit these functions to join the unit in 2012, and create this new team. He has obtained grants from the AFM, and has already recruited a post doc researcher. The positive impact of his supportive function for the other teams (generation of ad hoc iPS cells) is important, as well as ongoing collaborations concerning iPS cells induced into the neuronal dopaminergic subtype as a cellular therapy approach for Parkinson's disease treatment, which remains a challenging approach.

- Appreciation on the scientific strategy and the project

The proposed projects goals are:

- To understand the mode of action of the p38 pathway in mesoderm induction in ES cells. The team has shown that p38 acts on the stabilization of p53, a well-known protein involved in the regulation of cell proliferation, survival and differentiation. Undoubtedly the project proposed will favour understanding of p38/p53 crosstalk in the course of cellular fate commitment.

- To understand the way FoxO3 drives dopaminergic specialization of neurons, to obtain mouse iPS cells expressing a conditional FoxO3 protein in the context of both mouse progeria and neurodegenerative diseases (Parkinson's disease), and to develop cellular therapy to treat human neurodegenerescence by modulating FoxO3 activity. These ambitious projects will be performed with the expertise of the team in ES/iPS cells, and with internal or external expertise.

- To create, in collaboration with the other teams of the Unit, human iPS cell models for investigation and/or treatment of selected pathologies. Arrival of the team leader in the future Unit is undoubtedly of major interest for many projects in the Unit.

- Conclusion :

  – Summary

The results already obtained by the team in the culture and differentiation of human and mouse ES and iPS cells indicate a real expertise for the future Unit UMR_S 910 to develop iPS cells from fibroblasts of patients from several studied pathologies, allowing new potential cellular therapeutic avenues to cure studied pathologies.

Furthermore, the own ongoing projects of the team leader, dealing with the p38 MAPK mode of action in mesoderm induction in embryoid bodies through p53 stabilization, and with FoxO3 and dopaminergic neuron induction are well engaged, and already revealed in part their modes of action.

  – Strengths and opportunities

- Interesting project on p38 pathway in mesoderm induction, and on FoxO pathway in dopamine neurons

- Significant contribution to the investigation of progeria

- Above all, very useful supportive function for other teams in the stem cell field (ES & iPS cells)

– Weaknesses and threats

The team is small as compared with the other teams of the Unit, and has only one permanent researcher, the team leader.

– Recommendations

One or two permanent researchers should reinforce the group, otherwise it could be difficult to achieve all the projects proposed.

Team 9 : Genetics and Bio-informatics

Team Leader : Christophe BEROUD

- Staff members

	Past	Future
N1: Number of researchers with teaching duties (Form 2.1 of the application file)	1	1
N2: Number of full time researchers from research organizations (Form 2.3 of the application file)	1	1
N3: Number of other researchers including postdoctoral fellows (Form 2.2 and 2.4 of the application file)	✕	1
N4: Number of engineers, technicians and administrative staff with a tenured position (Form 2.5 of the application file)	✕	0
N5: Number of engineers, technicians and administrative staff without a tenured position (Form 2.6 of the application file)	4	5
N6: Number of Ph.D. students (Form 2.7 of the application file)	5	2
N7: Number of staff members with a HDR or a similar grade	2	2

- Appreciation on the results

This is a novel team, whose coming is conditional on the creation of a PU-PH position for C. Béroud. As such, the evaluation of previous results would normally be not applicable, but in this case, at least 3 team members (two researchers and one PhD) will move together from Montpellier, so the committee proposes to evaluate their previous work.

The bioinformatics team is heavily involved in developing LSDBs using a 4D database engine as well as setting up national collaborations on various diseases to collect genotype and detailed phenotype information using the LSDB tools on a national and international level. What differentiates this group's work from the other well known group (UMC, Leiden, NL) is the development in parallel of prediction tools to help understand the impact of variants on the phenotype (UMD Predictor and Human Splice Finder).

The team leader has had the difficult task to establish national networks of clinicians and geneticists on 9 different groups of rare diseases, convincing them to share data with colleagues from different disciplines as well as spend time on actually entering the data into his UMD database system. The team had thus a lasting impact on greatly improving the collaborative effort in those different groups.

The quality of the research is proven by extensive partnerships both at national and international levels as well as the peer reviewed publications. A large number of publications have been published in widely read journals such as Human Mutation, American Journal of Medical Genetics, European Journal of Medical Genetics. A large number of papers (13) have both researchers as authors, there are all together 41 different publications from either one or the

other researcher. They have been first and last co-authors on several publications as well as second and second last. Both have also participated as co-authors of various book chapters.

Another important aspect is their work as database curators for various LSDBs.

Researchers of team 9 have already published in collaboration with researchers of the unit. They are participating to common European projects.

- Appreciation on the impact, the attractiveness of the team and of the quality of its links with international, national and local partners

The team leader is communicating editor for the journal Human Mutation (since Feb.2008) as well as reviewer for: Human Mutation, Genes Chromosomes and Cancer, BMC Medical Informatics and Decision Making and several other journals. He is also board member of the HGVS and of its scientific committee, as well as expert of the Office of rare diseases Research (ORDR) of the NIH, expert for the European Commission on genetics, databases and rare diseases as well as member of the scientific committee on translational research of the French AFM.

The team comprised several PhD students, one of which will move to Marseille and continue as Post-doc. Although partner in various EU funded projects, recruitment was limited to national level at his past institution in Montpellier. The team will be well linked to several other teams in Marseille, this should increase its ability to recruit at international level.

The team participates in several EU funded projects, although not as coordinator (TREAT-NMD; GEN2PHEN; NMD-chip; BIO-NMD) This shows a capacity to persevere successfully in a very competitive environment,. The team also received funding through national granting agencies and various foundations and participated in various national consortia (funding through PHRC, ANR, AFM and many others).

The team established several networks to collect genotype phenotype information on various groups of diseases at a national level. The team also established research projects financed through a PHRC to recruit families presenting FID as well as gathered support from the French National Cancer Institute to support various national LSDBs on cancer related genes (e.g. BRCA1, BRCA2, MLH1, MSH2). The team is furthermore involved in other initiatives to establish LSDBs on other genes at the national level.

The team also established collaborations with the Canadian Marigold Foundation, the US Cure-CMD Foundation as well as the Jain Foundation to establish relevant international LSDBs (e.g. DNM2, MTM1, LAMA2, RYR1,…)

Several concrete results of the research activity are worth mentioning:

Software development

- UMD: a locus specific database to collect, manage and analyse genotypes and phenotypes relating to a given gene.

- Human Splicing Finder: a tool aimed at studying of the pre-mRNA splicing.

- GNALogique: a tool to draw genealogical trees

- Web site “Gene Table” at musclegenetable.org collecting information and links about genes related to neuromuscular disorders.

- a non referenced clinical data management system

Software use and applications

- LSDB curation

- Genotype based therapies: prediction and evaluation of potential exon skipping which could theoretically transform DMD into mild BMD

- Human genome annotation for example for NMDchip

Epidemiological, model animals, functional studies

- Exhaustive study of dystonia in France as well as with Poland and Algeria

- GWA identified a new highly probable locus.

- Preliminary results indicate more than one unassigned gene for FID (focal idiopathic dystonia).

- C. elegans model: on going validation of the model to link TOR1A with dystonias

- torsineA study in collaboration to understand its interaction with other molecules.

- Appreciation on the scientific strategy and the project

The team proposes to continue development of software tools (database as well as variant prediction support) as well as the discovery of a gene related to Dystonia, prospective European multi centre research studies on overweight and obesity, supporting the RADICO project by setting up French registries for various rare diseases (such as Pompe, Gaucher, chronic myeloid leukemia, and others).

Part of these projects have already funding for 2011 and 2012 (EU, ANR, AFM), based on the track record of the team, they are clearly feasible, they also integrate well into several aspects of the research done in the other teams.

The discovery of a gene for Dystonia, a candidate region of 40cM has been defined, if successful, could be an important step forward in understanding Dystonia.

- Conclusion :

– Summary

Although a new team in Marseille, several team members have already worked together and will move together to Marseille. The team works simultaneously on software aspects for molecular genetics and wet lab research such as discovery of new genes related to diseases. The team has already worked with several researchers of the future unit and should be quickly productive from the start.

– Strengths and opportunities

The team has a rather unique strength: the combination of bio-informatics expertise and wet lab research experience. The synergy allows the development of algorithms based on understanding of basic biological interactions at the DNA level, as well as fully exploiting data generated by wet lab experiments such as aCGH and next generation sequencing. The team already has secured funding for the future, including 3 bio-informatics engineers, several PhDs and postdocs.

– Weaknesses and threats

The only difficulty the team might face is the hiring of top-level computer scientists and bio-informatics engineer, as the competition with private companies and enterprises for these candidates is very high.

– Recommendations

The committee strongly recommend considering to recruit a computer scientist/informatics engineer at MSc or PhD level with interest in biology to complement the strength of the team with competences in software architecture and design. This should increase the team's long-term bio-info developments.

Intitulé UR / équipe	C1	C2	C3	C4	Note globale
GÉNÉTIQUE MÉDICALE ET GÉNOMIQUE FONCTIONNELLE	**A**	**A**	**A+**	**A**	**A**
TRANSLATIONAL MYOLOGY [LEVY-BARTOLI-KRAHN]	A	A	Non noté	A	A
GENETICS AND BIO-INFORMATICS [LEVY-BEROUD]	B	A	Non noté	B	B
EMBRYONIC STEM CELLS AND IPS [LEVY-BINETRUY]	B	B	Non noté	B	B
GENETICS AND PATHOPHYSIOLOGY OF AUTOSOMAL RECESSIVE NEUROLOGICAL DISORDERS [LEVY-DELAGUE]	B	B	Non noté	A	B
NUCLEAR ENVELOPE AND DISEASES [LEVY-LEVY]	A+	A+	Non noté	A+	A+
EPIGENETICS, CHROMATIN AND DISEASES [LEVY-MAGDINIER]	A	A	Non noté	A	A
AXONAL GROWTH AND NEURODEVELOPMENTAL DISORDERS [LEVY-MANN]	A+	A	Non noté	A+	A+
HUMAN NEUROGENETICS [LEVY-VILLARD]	A	A	Non noté	A	A
GENETICS AND DEVELOPMENT ON CARDIOVASCULAR DISORDERS [LEVY-ZAFFRAN]	A	A	Non noté	A	A

C1 Qualité scientifique et production

C2 Rayonnement et attractivité, intégration dans l'environnement

C3 Gouvernance et vie du laboratoire

C4 Stratégie et projet scientifique

Statistiques de notes globales par domaines scientifiques

(État au 06/05/2011)

Sciences du Vivant et Environnement

Note globale	SVE1_LS1_LS2	SVE1_LS3	SVE1_LS4	SVE1_LS5	SVE1_LS6	SVE1_LS7	SVE2 _LS3 *	SVE2_LS8 *	SVE2_LS9 *	Total
A+	7	3	1	4	7	6		2		30
A	27	1	13	20	21	26	2	12	23	145
B	6	1	6	2	8	23	3	3	6	58
C	1					4				5
Non noté	1									1
Total	**42**	**5**	**20**	**26**	**36**	**59**	**5**	**17**	**29**	**239**
A+	16,7%	60,0%	5,0%	15,4%	19,4%	10,2%		11,8%		12,6%
A	64,3%	20,0%	65,0%	76,9%	58,3%	44,1%	40,0%	70,6%	79,3%	60,7%
B	14,3%	20,0%	30,0%	7,7%	22,2%	39,0%	60,0%	17,6%	20,7%	24,3%
C	2,4%					6,8%				2,1%
Non noté	2,4%									0,4%
Total	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%

*** les résultats SVE2 ne sont pas définitifs au 06/05/2011.**

Intitulés des domaines scientifiques

Sciences du Vivant et Environnement

• SVE1 Biologie, santé
- **SVE1_LS1 Biologie moléculaire, Biologie structurale, Biochimie**
- **SVE1_LS2 Génétique, Génomique, Bioinformatique, Biologie des systèmes**
- **SVE1_LS3 Biologie cellulaire, Biologie du développement animal**
- **SVE1_LS4 Physiologie, Physiopathologie, Endocrinologie**
- **SVE1_LS5 Neurosciences**
- **SVE1_LS6 Immunologie, Infectiologie**
- **SVE1_LS7 Recherche clinique, Santé publique**

• SVE2 Ecologie, environnement
- **SVE2_LS8 Evolution, Ecologie, Biologie de l'environnement**
- **SVE2_LS9 Sciences et technologies du vivant, Biotechnologie**
- **SVE2_LS3 Biologie cellulaire, Biologie du développement végétal**

UNIVERSITÉ DE LA MÉDITERRANÉE
AIX-MARSEILLE II

Objet : Réponse au rapport d'évaluation - **S2UR120001654 - Génétique Médicale et Génomique Fonctionnelle - 0131843H** - de l'unité Génétique Médicale et Génomique Fonctionnelle

Observations d'Aix-Marseille Université

Team 3 (**Translational Myology - head : Marc Bartoli and Martin Krahn**) and team 5 (**Genetics and Pathophysiology of Autosomal recessive Neurological Disorders - head :Valérie Delague and André Megarbané**). are still part of the team led by Nicolas Lévy and some questions related to the future relationships have been raised and will be answered.
For team 3 in particular, some elements have been mis-perceived also because one of the co-leaders (Marc Bartoli) joined the lab and this particular team during the present period (2009). This made his list of previous achievements much less visible that deserved. Marc Bartoli's achievements were indeed mainly included in the "personal activity" file, not as parts of the main "past activities" and "project" documents.

TEAM 3 : TRANSLATIONAL MYOLOGY (M. BARTOLI/M. KRAHN)

Team 3 characterizes patients' cohorts as precisely as possible at the genetic level, and this has been valuated through different publications.
However, the journals publishing data on such cohorts do not have "major" impact factors, which is partially a reason for the "heterogeneous" publication report. However, such characterizations of the cohorts also allowed publishing high impact data (i.e. Krahn, Wein, Bartoli et al., 2010, Science Translational Medicine; Wein et al, Human Mutation), and we intend to continue this valorization of our patients' cohorts. The studies which led to publishing 2 independent therapeutic strategies in 2010 (Exon Skipping and AAV Gene-transfert) are part of pure translational research programs based on our cohorts.
This leads, indeed, to a heterogeneous publication record that we revendicate.

Marc Bartoli and Martin Krahn have a long background in Science/clinics and are well equiped for managing this new team. First of all, as reflected by the bibliometry corresponding to Marc Bartoli and his previous experience and background, this later may not be considered as a "young" researcher. Marc Bartoli (42 years old) has been hired with a CNRS (CR1) permanent position in 2010 but he had previously spent 8 years as a full time researcher at the Genethon institute. Prior to his position at Genethon, he had spent 3 years as a postdoc fellow at Harvard Medical school. He joined the laboratory during the previous quadriennal period and in the last 2 years, he exerted a pivotal role in the scientific management of the team, not only as a project leader, but also in terms of students'

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supervision and grants writing. His personal bibliometry, in particular the articles published prior his arrival in the team, were apparently not taken into account since they were presented only in the "individual activity" file. Martin Krahn and Marc Bartoli, wrote either alone or in collaboration several grant applications with success : ANR, AFM, FRM, Gis-maladies rares, Jain Foundation. They are also co-first author of a recent article published in Science Translational Medicine.

The respective implication of the two leaders is extremely clear and, in view of the translational topics of the team, co-leadership it seems particularly relevant. Martin Krahn is in charge of the patients and sample collections, cohorts constitutions, molecular explorations and genotype-phenotype correlations. He is in charge as PI of the project (Calpain and eosinophils*). Beside, he is strongly involved in all the fundamental research aspects, which will be led, in particular by Marc Bartoli. Their relationships with Nicolas Lévy are also extremely clear. They are now in charge of the projects of the team. Nicolas Levy will continue to participate to scientific discussions on these topics but will not orientate the scientific directions of any of this team's projects.

Concerning manpower, the team:
- is currently in the process of recruiting a post-doc candidate (who will defend his PhD work at the end of 2011);
- has a grant (starting fall 2011) for an additional PhD student through the international program MYOGRAD;
- has the financial support (through the AFM) to hire a technician for 4 years starting fall 2011.

TEAM 5 : GENETICS AND PATHOPHYSIOLOGY OF AUTOSOMAL RECESSIVE NEUROLOGICAL DISORDERS - HEAD : VALERIE DELAGUE/ANDRE MEGARBANE

It seems that some confusion has been unfortunately introduced concerning the relationships between the team 5 and the Inserm Associated International Lab (LIA). André Mégarbané is head of a Medical Genetics Unit lab (UGM), labelled as LIA Inserm. He has his own activities both at diagnosis and research level. It remains clear that Valérie delague has her own activities in research that she develops outside the context of the collaboration with André Mégarbané. Until the end of 2011, Valérie will remain a group leader in Nicolas Lévy's team and as such, she develops her own research projects, that will be pursued and implemented as a new team leader in the next research Unit. As for numerous other researchers in the field of human genetics, the basis of Valérie's research is the study of patients and families, and she will specifically study large consanguineous families, which originate from several countries (several collaborations apart the one with UGM), as well as families and patients cohorts that we study in close collaboration with the molecular diagnosis lab at La Timone Hospital. André Mégarbané, as part of the future research research team 5, should be seen as the integration of an "hospital-university" researcher, bringing his expertise in clinical genetics of rare (extremely rare and not yet nosologically defined), within the context of a translational research program. In this contexte, it is of extreme importance to take into account the fact that a large part of the team 5's research

program will be dedicated to the study of physiopathological mechanisms, taking advantage of the generated mice models.

Some projects are already running and will be pursued. In particular, the study of CMT4H physiopathology is one leading project with newly constructed models of KO mice (*fgd4*). As for other genes that would be identified in the future, some of the corresponding disorders will be further studied to address their pathophysiology and, if possible, identify therapeutic targets. Some others might be left aside, either due to certain difficulties or based on a pertinent selection and the adequation between the manpower and the projects size. Finally, in the context of pathophysiological studies, LIA also maintains number of collaborations with different laboratories in France and worldwide, who will perform the corresponding cellular an pathophysiological approaches when the genes have been identified based on their specific collaboration with André Mégarbané.

En accord avec les deux autres établissements d'Aix-Marseille

Le Président
de l'Université de la Méditerranée

Yvon BERLAND

Le Vice-président du Conseil Scientifique
de l'Université de la Méditerranée

Pierre CHIAPPETTA

Inserm
Institut national
de la santé et de la recherche médicale

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

APRIL, 5th, 2011

REPLY FROM NICOLAS LEVY (UMR_S 910)

TO THE

AERES report on the research unit
Génétique Médicale et Génomique Fonctionnelle
From the
Université d'Aix-Marseille 2
INSERM

Marseille, April the 4th, 2011

Dear Sir, Madam

We first want to thank the experts for their report which, in our view, reflects our feeling on the laboratory and its scientific content and context. This is true not only for the laboratory in general (scientific directions, strategy and management), but also for the scientific teams separately.

Most of the recommendations raised in the AERES report have already been corrected (postdoc hiring, ...) since they were planned even before the AERES on site visit. For team 1, we just want to point out that 2 full time researchers (not 1) are included (Laurent Villard - DR2/Inserm and Jean-Christophe Roux - CR1/Inserm).

*Thus, in the present document, the comments which will be addresed concern exclusively the evaluation performed for team 3 (**Translational Myology - head : Marc Bartoli and Martin Krahn**) and, on another hand, the evaluation performed regarding the team 5 (**Genetics and Pathophysiology of Autosomal recessive Neurological Disorders - head : Valérie Delague and André Megarbané**).*

Indeed, these 2 teams are still part of the team led by Nicolas Lévy and we perfectly understant that some questions related to the future relationships may be raised. We feel that, for team 3 in particular, some elements have been mis-perceived (again due to the fact that this team is issued from Nicolas Levy's team), and also because one of the co-leader (Marc Bartoli) joined the lab and this particular team during the present period (2009). This made his list of previous achievements much less visible that deserved. Marc Bartoli's achievements were indeed mainly included in the "personal activity" file, not as parts of the main "past activities" and "project" documents.

TEAM 3 : TRANSLATIONAL MYOLOGY (M. BARTOLI/M. KRAHN)

This team was favourably evaluated from the scientific point of view (project), as well as regarding the past activities. We thank the experts for their important and positive expertise. However, we somehow disagree with some comments or, at least, would like to comment on some pointed criticisms.

Weaknesses and threats

Below, 3 points enlisted by the experts have been addressed and replied. The 4th point (**>- Scientific autonomy not yet established (most topics set up by Nicolas Levy)**) will be addressed in the recommendations' section (**>- Codify the respective implication of the two leaders and their relationships with Nicolas Levy**).

> - Heterogeneous publication record

We thank the reviewer for pointing out as a strength and opportunity of our team the fact that we have constituted important cohorts of rare diseases governed by MDs involved in the team.

We would like to underline that we try to characterize these cohorts as precisely as possible at the genetic level, and this has been valuated through different publications. However, the journals publishing data on such cohorts do not have "major" impact factors, which is partially a reason for the "heterogeneous" publication report. However, such characterizations of the cohorts also allowed publishing high impact data (i.e. Krahn, Wein, Bartoli et al., 2010, Science Translational Medicine; Wein et al, Human Mutation), and we intend to continue this valorization of our patients' cohorts. We would also like to point out that the studies which led us to publishing 2 independant therapeutic strategies in 2010 (Exon Skipping and AAV Gene-transfert) are part of pure translational research programs based on our cohorts, and we are happy to publish also the 1st steps of these programs, (and not only the final therapeutic steps). This leads, indeed to a heterogeneous publication record that we revendicate.

> - Insufficient manpower

We would like to underline that:

- we are currently in the process of recruiting a post-doc candidate (who will defend his PhD work at the end of 2011)
- we have a grant (starting fall 2011) for an additional PhD student through the international program MYOGRAD in which we are implicated
- we have the financial support (through the AFM) to hire a technician for 4 years starting fall 2011

> - Young bicephalous group with little experience in management

We agree with the reviewer that this team is young as it is the result of the spliting of Nicolas Lévy previous team into 3 different teams. However, Marc Bartoli and Martin Krahn have a long background in Science/clinics. We would like to pinpoint some aspects of their experience that may suggest that they are well equiped for managing this new team. First of all, as reflected by the bibliometry corresponding to Marc Bartoli and his previous experience and background, this later may not be considered as a "young" researcher. Marc Bartoli (42 years old) has been hired with a CNRS (CR1) permanent position in 2010 but he had previously spent 8 years as a full time researcher at the Genethon institute. Prior to his position at Genethon, he had spent 3 years as a postdoc fellow at Harvard Medical School (lab of Jonathan Cohen) (See J. Biol. Chem, 2001).

He joined our laboratory during the previous quadriennal period and in the last 2 years, he exerted a pivotal role in the sicientific management of the team, not only as a project leader, but also in terms of students' supervision and grants writing. His personal bibliometry, in particular the articles published prior his arrival in the team, were apparently not taken into account since they were presented only in the "individual

activity" file (this list is attached below). As it is now more visible, Marc authored most of the articles either as a first author (5 out of 10) or as a senior/co-senior author. In his previous lab, the rule was that the team leader signed all the articles in last author's position. During his period at Genethon, he supervised two assistants' engineer (Nathalie Bourg-Alibert; Carinne Roudaut) for bio experimentation and in vivo imaging and a senior technician (Jérôme Poupiot) for studies on gene transfer and control of the immune response. He also co-supervised 3 PhD students (Lydie Laure, William Lostal and Tayebeh Soheili).
Currently, Marc Bartoli and Martin Krahn supervise two PhD students : Florian Barthelemy (2nd year) and Virginie Kergourlay (1st year) and several students in master 1 and 2. Their tasks are to establish the strategy to identify key issues that we want to address and daily monitor the progress of their work. Marc also contributes to most of the imaging studies, DNA-chip and data analysis, and he advises students and engineers for molecular and cellular biology and protein biochemistry. He also, together with Valérie Delague, organized the English Spoken Team Meeting (1-2 sessions each month) to improve student spoken skills in English and to share technical hurdles and strategic questions. Martin Krahn as a MCU-PH is involved in teaching to medical students he is responsible of the genomics module in the "M2 tronc commun" and co-responsible of the "modules" "cellules souches et thérapies innovantes" and "mécanisme de survenue des maladies génétiques".
Martin Krahn and Marc Bartoli, wrote either alone or in collaboration several grant applications with success : ANR, AFM, FRM, Gis-maladies rares, Jain Foundation. They are also co-first author of a recent article published in Science Translational Medicine.
Finally, recently, Marc Bartoli has authored one article as last author in the team (Eur. J. Hum. Genet). He is also the last author in an article in press (Molecular Medicine, Impact Factor : 5.32). Martin Krahn is also the last author of an article issued from the group (in press).
Finally, we want to emphasize that "Bicephaly" may, in some instances be an advantage. In this particular case, it allows to bring a legitimity toward raising funds issued from both clinical research and fundamental calls.

Recommendations

>- Engage active recruitment of post-doc and PhD students
This point has been addressed above and is repeated here below :
- we are currently in the process of recruiting a post-doc candidate (who will defend his PhD work at the end of 2011)
- we have a grant (starting fall 2011) for an additional "non French" PhD student through the international program MYOGRAD in which we are implicated.
- we have the financial support (through the AFM) to hire a technician for 4 years starting fall 2011

>- Efforts to reach a generally higher level of publication are necessary

See comments above (Translational Research). We are confident that, according to the curent projects on Dysferlin and FSHD in particular, the team will reach these expectations.

>- Codify respective implication of the two leaders and the relationships with Nicolas Levy

The respective implication of the two leaders is extremely clear and, in view of the translational topics of the team, it seems particularly relevant. Martin Krahn is in charge of the patients and sample collections, cohorts constitutions, molecular explorations and genotype-phenotype correlations. He is in charge as PI of the project (Calpain and eosinophils*). Beside, he is strongly involved in all the fundamental research aspects, which will be led, in particular by Marc Bartoli. It is important to note that Marc and Martin have a long time experience in working together, including the co-management of projects and students. Martin was a former postdoc fellow at Genethon institute (starting 2006) where he started to work together with Marc Bartoli. This was also one of the reasons why Marc decided to join the lab in Marseille. Since, their collaboration has been fruitful from a pure scientific point of view as well as it lies on an extremely positive climate of human cooperation. In brief, Marc and Martin have not accepted the co-direction of team3... They required it!

Their relationships with Nicolas Lévy are extremely clear. They are now in charge of the projects of the team. Not Nicolas Levy! This later will continue to participate to scientific discussions on these topics but will not orientate the scientific directions of any of this team's projects, nor he will manage students or write related grants! All these duties will be those of the team leaders. This point was probably not clear enough during the AERES on site visit since team 3 has just emerged as a new team, and this will become official starting january 2012.

*NB : In the AERES report, this project has been, by error, attributed to the actual team 1 (Laurent Villard). Actually, this project was headed by team 2 (Nicolas Levy) and Martin Krahn is the 1st author of the princeps paper on this topic (Annals of Neurology, 2006). He is also the 1st author of the recently published and collaborative article (Krahn et al, 2011).

Marc Bartoli Bibliography 2006-2010 (not including the publications issued from his work after he joined UMR_S 910) :

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A. Milic, N. Danièle, H. Lochmüller, M. Mora, G. Comi, M. Moggio, F. Noulet, J. Poupiot, C. Roudaut, **M. Bartoli** and I. Richard. "A third of LGMD2A biopsies have normal calpain 3 proteolytic activity as determined by an in vitro assay" Neuromuscular Disorders (2007), 2: 148-56.

M. Bartoli, C. Roudaut, S. Martin, F. Fougerousse, L. Suel, J. Poupiot, E. Gicquel, F. Noulet, O. Danos and I. Richard. "Safety and efficacy of AAV-mediated calpain 3 gene transfer in a mouse model of limb-girdle muscular dystrophy type 2A." Molecular Therapy. (2006) 13: 250-259.

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M. Bartoli*, N. Bourg*, D. Stockholm*, F. Raynaud, N. Armande, and I. Richard “A mouse model for monitoring calpain activity under physiological and pathological conditions” J. Biol Chem. (2006) 281(51):39672-80.

TEAM 5 : GENETICS AND PATHOPHYSIOLOGY OF AUTOSOMAL RECESSIVE NEUROLOGICAL DISORDERS - HEAD : VALERIE DELAGUE/ANDRE MEGARBANE

This team was favourably evaluated from the scientific point of view (project), as well as regarding the past activities. We thank the experts for their important and positive expertise. However, we wish to clarify specific points regarding the relationships between the team and the international lab, as well as their respective directors (both being team 5 co-leaders). The team's strategy will be also clarified.

Weaknesses and threats

>- Although the high quality of previous research and publications of the collaborative work are evident, one could raise doubts concerning the clear strategy of the team independently form the associated international unit.

Although the positive evaluation in terms of scientific quality of the research group headed by Valerie Delague on the one hand, and also based on a long time collaboration with André Mégarbané on the other hand, it seems that some confusion has been unfortunately introduced concerning the relationships between the team 5 and the Inserm Associated International Lab (LIA), and we understand that some of the messages were not delivered in a clear enough way during the visit. André Mégarbané is head of a Medical Genetics Unit lab (UGM), for which we have obtained the label as LIA Inserm. He has his own activities both at diagnosis and research level. Although we have extremely close collaborations for many years, It remains clear that Valérie delague has her own activities in research that she develops outside the context of the collaboration with André Mégarbané. Until the end of 2011, Valérie will remain a group leader in Nicolas Lévy's team and as such, she develops her own research projects, that will be pursued and implemented as a new team leader in the next research Unit. As for numerous other researchers in the field of human genetics, the basis of Valérie's research is the study of patients and families, and she will specifically study large consanguineous families, which originate from several countries (several collaborations apart the one with UGM), as well as families and patients cohorts that we study in close collaboration with the molecular diagnosis lab at La Timone Hospital. André Mégarbané, as part of the future research research team 5, should be seen as the integration of an "hospital-university" researcher, bringing his expertise in clinical genetics of rare (extremely rare and not yet nosologically defined), within the context of a translational research program. In this contexte, it is of extreme importance to our view to take into account the fact that a large part of the team 5's research program will be dedicated to the study of physiopathological mechanisms, taking advantage of the generated mice models.

Recommendations

>- To identify clearly the leadership of the team in which some members (including the Head) of the Beirut Inserm International Associated Lab would be included.

The team will be headed by Valérie Delague, who will provide scientific directions to the team's research projects, including the models to be developed, the recruitment of students, the grants applications, etc… André Mégarbané will be part of the team as an "hospital-university" researcher in other teams. Another member from the International Associated Lab, is a research engineer, who is implicated in several projects of gene identification. In summary, the team 5 headed by Valérie Delague, will base several projects on the close cooperation with the LIA, this later being headed by André mégarbané.

>- To highlight the pathophysiological studies of the team, which are specifically directed on former and future genes identified in collaboration with the international associated lab.

Some projects are already running and will be pursued. In particular, the study of CMT4H physiopathology is one leading project with newly constructed models of KO mice (*fgd4*). As for other genes that would be identified in the future, some of the corresponding disorders will be further studied to address their pathophysiology and, if possible, identify therapeutic targets. Some others might be left aside, either due to certain difficulties or based on a pertinent selection and the adequation between the manpower and the projects size. Finally, in the context of pathophysiological studies, our LIA also maintains number of collaborations with different laboratories in France and worldwide, who will perform the corresponding cellular an pathophysiological approaches when the genes have been identified based on their specific collaboration with André Mégarbané.

Professeur Nicolas LEVY
Directeur de l'UMR_S 910