Research evaluation

EVALUATION REPORT OF THE UNIT
Centre de recherche en Myologie

UNDER THE SUPERVISION OF THE FOLLOWING ESTABLISHMENTS AND ORGANISMS:

Sorbonne Université,
Institut national de la santé et de la recherche médicale – Inserm

EVALUATION CAMPAIGN 2023-2024
GROUP D

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High Council for evaluation of research and hignter education

In the name of the expert committee[1] :

Laurent Schaeffer, Chairman of the committee

For the Hcéres[2] :

Stéphane Le Bouler, acting president

Pursuant to Articles R. 114-15 and R. 114-10 of the French Research Code, evaluation reports drawn up by expert committees are signed by the chairmen of these committees and countersigned by the President of Hcéres.

To make the document easier to read, the names used in this report to designate functions, professions or responsibilities (expert, researcher, teacher-researcher, professor, lecturer, engineer, technician, director, doctoral student, etc.) are used in a generic sense and have a neutral value.

This report is the result of the unit's evaluation by the expert committee, the composition of which is specified below. The appreciations it contains are the expression of the independent and collegial deliberation of this committee. The numbers in this report are the certified exact data extracted from the deposited files by the supervising body on behalf of the unit.

MEMBERS OF THE EXPERT COMMITTEE

Chairperson:	Mr Laurent Schaeffer Université Claude Bernard Lyon 1 - UCBL
Experts:	Ms Agnès Castan Inserm - Institut national de la santé et de la recherche médicale (supporting personnel) Ms Maud Frieden Université de Genève Suisse Ms Lucie Carrier University Medical Center Hamburg-Eppendorf Allemagne Mr Philippe Couratier Centre Hospitalier Universitaire de Limoges Ms Nadine Laguette Centre national de la recherche scientifique - CNRS Mr Philippos Mourikis Centre national de la recherche scientifique - CNRS Mr Antonio Musaro Sapienza University of Rome Italie Mr Marco Sandri Department of Biomedical Sciences, University of Padova Italie Mr Krzysztof Sobczak Adam Mickiewicz University Poznan Pologne

HCÉRES REPRESENTATIVE

Ms Marie-Paule Roth

REPRESENTATIVES OF SUPERVISING INSTITUTIONS AND BODIES

Mr Thierry Galli, Institut Thématique Biologie cellulaire, Développement et Evolution, Inserm

Ms Anne-Geneviève Marcelin, Vice-Doyenne Recherche, Sorbonne Université

Ms Jacqueline Capeau, Chargée de Mission, Faculté de Santé, Sorbonne Université

CHARACTERISATION OF THE UNIT

- Name: Centre de recherche en Myologie
- Acronym: CRM
- Label and number: U974
- Composition of the executive team: Bertrand Fontaine, Director Denis Furling, Deputy Director

SCIENTIFIC PANELS OF THE UNIT

SVE Sciences du vivant et environnement
SVE6 Physiologie et physiopathologie humaine, vieillissement
SVE5 : Neurosciences and Nervous System Disorders
SVE7: Prevention, Diagnosis and Treatment of Human Diseases

THEMES OF THE UNIT

The general scientific aim of the CRM, a monothematic and multi-team research unit, is to understand striated muscle biology within its healthy or pathological environment and to improve treatments for patients with neuromuscular disorders. The scope of the CRM ranges from fundamental research to pathophysiology and preclinical strategies, from bench to bedside.
The research themes developed in the CRM are:

- Biology, genetics and pathophysiology of nuclear matrix and associated pathologies
- Muscle mass and function maintenance
- Optimisation of AAV-based gene therapies
- Muscle cell organisation and therapy of dominant centronuclear myopathy
- Pathophysiology and therapy of type 1 myotonic dystrophy
- Cell and molecular orchestration in muscle regeneration, ageing and diseases
- Epigenetics and biotherapies of motor neuron disorders
- Myasthenia gravis: etiology, pathophysiology and therapeutic approaches
- Muscle Inflammation: targeted and innovative therapeutics
- Neuromuscular connectivity in health and diseases

HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

The Centre of Research in Myology (CRM) The CRM is housed in the Pitié-Salpêtrière Hospital, one of the largest European University Hospitals run by the 'Assistance Publique-Hôpitaux de Paris' (AP-HP). It is a mixed research unit (UMRS974) created in 2014 by Sorbonne University (SU), the National Institute of Health and Medical Research (Inserm) and the Association Institute of Myology (AIM) founded by the French Muscular Dystrophy Association (AFM-Téléthon) in 2005. The CRM is also part of the Institute of Myology (IM) founded in 1996 as a partnership between AFM-Téléthon and five public institutions, SU (University Pierre and Marie Curie at that time), INSERM, CNRS (Centre National de la Recherche Scientifique), CEA (Commissariat à l'énergie atomique) and AP-HP (Assistance Publique-Hôpitaux de Paris), to accelerate clinical research for the benefit of patients affected by neuromuscular disorders.
The CRM is implanted in the Pitié-Salpêtrière Hospital, under the responsibility of the Faculty of Medicine of SU. Since its creation, the CRM has been housed in two separate locations within the Pitié-Salpêtrière University Hospital site. Half of the unit is in the Babinski building and the other half in the Faculty of Medicine (building 105), 700 metres apart.

RESEARCH ENVIRONMENT OF THE UNIT

The CRM is part of the research units located on the Pitié-Salpêtrière campus. They are dedicated to neurology (Brain and Spine Institute, ICM), cardio-metabolism (Institute of Cardio-Metabolism and Nutrition, ICAN), immunology (Centre for Immunology and Infection, CIMI), and respiration (Respiratory Neurophysiology Laboratory, UMRS1158). Several state-of-the-art university-run technical platforms are available on site, grouped within mixed service units (UMS). The CRM also benefits from the clinical environment of the Pitié-Salpêtrière hospital that is structured in clinical departments with the support of a methodology and epidemiology centre unit for clinical research (IPLESP). The CRM is tightly linked with the medical departments, especially the Neuromyology unit, directed by the current director of the CRM, which includes the North/East/Ile-de-France neuromuscular disease reference centre, with active files for more than 3,000 patients per year, providing detailed data and precious biomaterials for research. The leader of team 9 (Muscle and Inflammation) is in charge of the department of internal medicine and clinical immunology.
The CRM is also part of the Institute of Myology (IM) currently based on a partnership between the AIM and public partners including SU, INSERM and AP-HP, and benefits from this environment. IM represents a public-private partnership creating a large critical mass of clinicians and researchers, gathering 300 muscle experts

focused on diagnosis, medical care, functional evaluation, basic, applied, clinical and translational research for patients and their families, as well as teaching. IM brings together the Service of Neuromyology, the CRM and AIM resources gathering the Neuromuscular Investigation Centre (which includes an NMR and spectroscopy laboratory, a morphology unit, a patient registry/database unit and a neuromuscular physiology laboratory), the Myobank-AFM human tissue collection for research, as well as paediatric and adult clinical trial Centres. In addition, IM is also a component of the AFM-Téléthon network, which associates the laboratories of Généthon and iStem (Évry).

UNIT WORKFORCE: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	7
Maîtres de conférences et assimilés	2
Directeurs de recherche et assimilés	15
Chargés de recherche et assimilés	16
Personnels d'appui à la recherche	35
Sous-total personnels permanents en activité	**75**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	25
Post-doctorants	19
Doctorants	22
Sous-total personnels non permanents en activité	**66**
Total personnels	**141**

DISTRIBUTION OF THE UNIT'S PERMANENTS BY EMPLOYER: in physical persons at 31/12/2022. Non-tutorship employers are grouped under the heading 'others'.

Nom de l'employeur	EC	C	PAR
Inserm	0	18	4
AUTRE	2	8	18
SORBONNE UNIVERSITÉ	7	0	7
APHP	0	0	12
CNRS	0	5	0
Total personnels	**9**	**31**	**41**

GLOBAL ASSESSMENT

CRM is part of the Institute of Myology, a corner stone of research in Myology in France. As of December 2022, the CRM workforce is composed of ten teams and hosts 148 persons including 35 researchers, 50 technicians/research assistants and associates, fourteen post-doctoral fellows, 21 PhD students and 21 clinicians. The general scientific aim of the CRM, a monothematic and multi-team research unit, is to understand the striated muscle biology within its healthy or pathological environment and to improve treatments for patients with neuromuscular disorders. The scope of the CRM ranges from fundamental research to pathophysiology and preclinical studies, from bench to bedside. The scientific goals of the Centre benefit from solid interactions with clinical environment and AIM entities. The CRM adopted the strategy to avoid overlap between their own platforms and those at the university/neighbour institutions. The CRM has developed excellent state-of-the-art technological platforms dedicated to cell culture, microscopy and vectorology. The platform dedicated to bioinformatics needs to be further developed.

The amount of funding of the CRM is outstanding, with an annual budget that has evolved from approximately 6 to 10 million euros, 49% coming from the AIM/AFM. 23 ANR contracts, including thirteen as coordinators and three ANR JCJCJ, were obtained.
Five funding from the European Union have been obtained as partners. (H2020 Solve-RD project, ANR E-Rare and Horizon Europe Era-MG Permed). Although significant, with a total of more than 1 million euros, European funds remain modest in the total budget of the CRM.
Despite the complexity of the period and perspectives of restructuration, the teams managed to increase their productivity. The number of patents (12) and publications has increased compared to the last evaluation to range from very good to excellent.
Scientific production is vey good to excellent with 638 articles were published in peer-reviewed journals with 40% signed in first, last or corresponding author. Particular attention was paid to increase the quality of scientific production with publications in high impact journals such as Mol Cell, JBC, Lancet Rhumato, Nat Commun…..
The CRM has embraced the question of scientific integrity. A researcher of the CRM participates in the development of the INSERM LORIER program and will be the CRM scientific integrity referent.
The attractiveness of the CRM is excellent, as evidenced by the involvement of the CRM in national and international neuromuscular networks, invitations to meetings and meeting organisations. During the 2017–2022 period, the CRM hosted 58 PhD students, including twelve non-French students, and 34 post-docs, among whom eighteen were from abroad. Thirty-nine PhDs were defended for 36 HDR. The recruitment of post docs remains a point to ameliorate.
Partnerships with industry have significantly increased to become outstanding. Two CIFRE doctoral fellowships were obtained with Sanofi and Servier. Collaborative projects have been carried out for drug design and synthesis, co-developments with the teams have been carried out with Benitec Biopharma, Pfizer, Sarepta, Biogen, Ahead Therapeutics, or Shire®. Several services contracts were signed, and six clinical trials were funded by private pharmaceutical companies, such as the Phase II/III for the treatment of the Inclusion Body Myositis.
The links with the non-academic world that were already excellent have been further strengthened (hosting college and high school students for short research discovery internships, interactions with patients and their families through AFM-Téléthon and AIM, scientific dissemination through Téléthon, 'Fête de la Science '', "Pint of Science"). The unit has increased its participation in community outreach activities at several levels, creating and using new "social" tools.
The CRM is recognised at the international level and is globally an excellent centre.

DETAILED EVALUATION OF THE UNIT

A – CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

The revisions made in response to the previous criticisms have significantly improved the overall quality of the centre. The centre provided a detailed response outlining the measures taken to address the criticisms raised during the review process.
The following items have been strengthened:

1) Several funding from the European Union have been obtained during the last mandate.
2) The number of patents and publications has increased with particular attention on the quality of scientific production rather than strictly quantitative indicators linked to the reputation of journal.
3) Partnerships with industry has increased
4) The links with the non-academic world have been maintained and strengthened (hosting college and high school students for short research discovery internships, interactions with patients and their families through AFM-Téléthon and AIM, scientific dissemination through Téléthon, 'Fête de la Science ", "Pint of Science").
5) The unit has increased its participation in community outreach activities at several levels, creating and using new "social" tools
6) The Centre offered different permanent staff members positions in teams. 4 technical staff have been recruited to support the teams
7) Internal collaborations among teams have been improved
8) The unit adopted the strategy to avoid overlap between their own platforms and those at the university/neighbour institutions.
9) The Centre pays attention to improve the welcome of newcomers, who receive training from the referents.
10) Mentoring by team leaders, towards post-docs and PhD students, has been improved
11) A grant office has been created in 2020.
12) The centre improved the focus of its scientific activity.

Some aspects still need improvement:

1) Although significant, with a total of more than 1 million euros, European funds remain modest in the total budget of the CRM
2) The recruitment of post docs remains a critical point
3) Although the CRM has established international collaboration, it is recommended that the different teams further strive for more national and international collaboration
4) The process related to the reunification of CRM in one building has been started in 2023. It is in progress but not finalised yet.
5) Administrative staff should be improved to increase support for the young researchers or technical staff.
6) The website of the research teams should be updated.
7) The intranet is still under construction.

B – EVALUATION AREAS

Considering the references defined in the unit's evaluation guidelines, the committee ensures that a distinction is made on the outstanding elements for strengths or weaknesses. Each point is documented by observable facts including the elements from the portfolio. The committee assesses if the unit's results are consistent with its activity profile.

EVALUATION AREA 1: PROFILE, RESOURCES AND ORGANISATION OF THE UNIT

Assessment on the scientific objectives of the unit

The scientific objectives are to carry out fundamental and translational research to i) better understand the biology of striated muscles including the neuromuscular system from the motor neuron to the skeletal and cardiac muscle, and ii) diagnose and develop therapeutic approaches for acquired and genetically caused neuromuscular disorders to improve patients' quality of life and expectancy.
The scientific goal of the Centre is also reached by strong interactions with the clinical environment and AIM entities. All teams comply with the objectives of the CRM.

Assessment on the unit's resources

The CRM host 148 members and three important technological platforms. Its annual budget is huge. It has evolved from approximately 6 to 10 million euros over the five-year period. Almost half of the budget is provided by AIM.

Assessment on the functioning of the unit

The CRM has a classic organisation adapted to the size of the centre. Its executive and advisory bodies have well-defined functions. It is run by the direction team (director and deputy director) and a Chief Administrative Officer.

1/ The unit has set itself relevant scientific objectives.

Strengths and possibilities linked to the context

The scientific goal of the Centre benefits from solid interactions with clinical environment and AIM entities. This is particularly important for the translational aspects of the CRM. Several proof-of-concept of RNA-based or gene therapies have already been validated at the preclinical level. Drug repositioning and cell therapy approaches developed by the teams have also reached clinical trials level, confirming the translational power and capacity of the research strategy at the CRM.
The CRM also benefits of excellent state-of-the-art technological platforms dedicated to cell culture, microscopy, vectorology and molecular biology

Weaknesses and risks linked to the context

Since its creation the CRM is located in two buildings of the Salpétrière 700 m apart from each other. This limits possibilities of interactions between the teams.
Although clearly in progress during the period, transversal collaborations among the CRM teams have remained limited with only 11% of the publications resulting from internal collaborations.

2/ The unit has resources that are suited to its activity profile and research environment and mobilises them.

Strengths and possibilities linked to the context

The CRM features

1) 35 researchers, 21 clinicians, 50 technicians/research associates and assistants, fourteen post-docs and 21 PhD students are organised in ten teams, three platforms and administrative and research support staff;more specifically seven INSERM researchers, four CNRS researchers and one PU-PH (two teams are each co-lead by 1 INSERM and 1 CNRS researchers). Moreover, the technical staff of the CRM is stronger than in most French laboratories. Among them, 27 have non-permanent positions, fifteen are supported by AIM/AFM funding, and 23 have permanent positions, eight are employed by the academic host institutions (4 INSERM and 4 SU) and the fifteen others are employed by AIM.
2) outstanding financial resources, with an annual budget ranging from 6 to 10 million euros. The funding is notably successful in securing national grants, having obtained 23 ANR grants during the term.

In terms of human resources, the CRM excels with a technical staff of 50 full-time equivalents.

Weaknesses and risks linked to the context

Forty-nine percent of the funding is provided by AIM and therefore relies on the yearly success of the Telethon.
The number of competitive European projects as coordinator is low.
The university only provides 12% of the CRM personnel.
Only three FTE are dedicated to the administration.

3/ The unit's practices comply with the rules and directives laid down by its supervisory bodies in terms of human resources management, safety, environment, ethical protocols and protection of data and scientific heritage

Strengths and possibilities linked to the context

Since the future director has been appointed deputy director, the functioning of the CRM has greatly improved with regards to communication and the implementation of different dedicated groups (steering committee, communication, equipment…). Its executive and advisory bodies have well-defined functions. The direction team meets on a weekly basis, manages current affairs and prepares meetings of the Steering committee and Laboratory Council.
Within the Institute of Myology, AIM has created a grant office to facilitate the search for funding by the teams.
The opportunity to consolidate all CRM teams in the same building is anticipated in the upcoming term. The reunification of CRM teams will require a budget exceeding 4 million euros, primarily funded by SU for the renovation of the premises, scheduled to commence in 2024.

Weaknesses and risks linked to the context

Inserm is in charge of an important part of the administrative work of CRM regarding contracts and recruitments. Teams leaders complain about the great lack of reactivity of the Inserm delegation in charge of CRM, which put some fundings at risk and creates a lot of inerty. Several postdocs and PhD students have reported that they worked for several months without a salary because of this situation, which is not acceptable.
The administrative staff of the CRM involves only three FTE, which is low for this size of the centre.
The current situation with AIM/Myology Foundation and the fact that discussions are ongoing with CRM governing bodies (Inserm and SU) fragilizes the CRM members. The absence of a common strategy shared by the partners (Inserm, Sorbonne University, APHP and AIM) makes it difficult for the staff to envision their future.
The CRM teams are still located in two different buildings located 700 metres apart of each other.

EVALUATION AREA 2: ATTRACTIVENESS

Assessment on the attractiveness of the unit

The attractiveness of the CRM is excellent, as evidenced by the involvement of the CRM in national and international neuromuscular networks.
CRM attractiveness greatly benefits from the proximity with the clinical units dedicated to neuromuscular disorders at the Pitié Salpétrière hospital. Altogether, the CRM has demonstrated a strong potential for translational activities.
The high level of funding of the CRM and the research teams (mainly by AIM and ANR) also contributes to the attractiveness of the CRM.
The structuration of three internal technological platforms respectively dedicated to immortalization of human cells (MYOLINE), microscopy (MYOIMAGE), and vectorology (MYOVECTOR), as well as platforms in the vicinity of the CRM, contribute to its attractiveness. During the 2017–2022 period, the CRM hosted 58 PhD students, including twelve non-French students, and 34 post-docs, among whom eighteen were from abroad.

1/ The unit has an attractive scientific reputation and is part of the European research area.

2/ The unit is attractive because for the quality of its staff support policy.

3/ The unit is attractive through its success in competitive calls for projects.

4/ The unit is attractive for the quality of its major equipment and technical skills.

Strengths and possibilities linked to the context for the four references above

The CRM enjoys international visibility in the neuromuscular area.
Five funding from the European Union have been obtained as partners. (H2020 Solve-RD project, ANR E-Rare and Horizon Europe Era-MG permed). Although significant, with a total of more than 1 million euros, European funds remain modest in the total budget of the CRM.
During the 2017–2022 period, the CRM hosted 58 PhD students, including twelve non-French students, and 34 post-docs, among whom eighteen were from abroad. Thirty-nine PhDs were defended for 36 HDR.

49%of funding is coming from the AIM/AFM. In addition, 23 ANR contracts (13 as coordinators), including three ANR JCJCJ (MotorDM, MAGENTA, Camanai), were obtained. One 'Équipe labélisée FRM' was obtained.
The Centre is situated within the hospital Pitié Salpêtrière in close proximity to clinicians. There is a robust potential for translational activities directed towards patients, supported by state-of-the-art technological platforms and access to various bioinformatics platforms. The forthcoming launch of the Myology Foundation has the potential to further enhance the CRM's national and international prominence. The structuration of three internal technological platforms respectively dedicated to cell culture (MYOLINE), microscopy (MYOIMAGE), and vectorology (MYOVECTOR), as well as platforms in the vicinity of the CRM, contribute to its attractiveness.

Weaknesses and risks linked to the context for the four references above

The involvement of CRM members as coordinators of international programs, especially EU programs is low and could be improved. Members are located in two distant buildings. French salaries for foreign postdocs and students are not attractive at the international level, especially for Paris where living is expensive.

EVALUATION AREA 3: SCIENTIFIC PRODUCTION

Assessment on the scientific production of the unit

The overall scientific production of the CRM has been very good to excellent.
Between 2017 and 2022, the CRM has produced 638 articles in peer-reviewed journals (554 original articles and 80 reviews). The number of articles in leading positions represented 40% of the CRM production (254 articles out of 638) in Lancet Rheumatology, Nature Biomedical Engineering, Science Translational Medicine, Nature Communications…

1/ The scientific production of the unit meets quality criteria.

2/ The unit's scientific production is proportionate to its research potential and properly shared out between its personnel.

3/ The scientific production of the unit complies with the principles of research integrity, ethics and open science. It complies with the directives applicable in this field.

Strengths and possibilities linked to the context for the three references above

The CRM has significantly increased the number of publications in journals with a large audience. 638 articles were published in peer-reviewed journals with 40% signed in first, last or corresponding author. The CRM has significantly increased the number of publications where researchers of the CRM are first, last or corresponding author in journals with a large audience such as Lancet Rheumatology, Nature Biomedical Engineering, Science Translational Medicine, Nature Communications, Molecular Cell, Journal of Clinical Investigations, Brain, Journal of Cell Biology, Acta Neuropathologica. Eleven percent of the publications were co-signed by members of different teams.
Regarding scientific integrity, ethics and open science, the CRM follows the rules of its academic bodies, INSERM and Sorbonne University.
A researcher of the CRM participates in the development of the INSERM LORIER program (organisation for Ethical and Responsible research) and will be the CRM scientific integrity referent.

Weaknesses and risks linked to the context for the three references above

Only 11% of articles involving members of several CRM teams. The proportion of articles in the most prestigious journal remains modest.

EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

Assessment on the inclusion of the unit's research in society

The level of valorisation is exceptional, with twelve patents and about twenty Industrial partnerships, with 6 clinical trials. These collaborations encompass joint projects and co-developments, accompanied by substantial financial support from industrial partners. Additionally, these interactions result in service contracts and contribute to the training of young researchers through two CIFRE doctoral fellowships.

1/ The unit stands out for the quality and the amount of its interactions with the non-academic world.

2/ The unit develops products for the cultural, economic and social world.

3/ The unit shares its knowledge with the general public and takes part in debates in society.

Strengths and possibilities linked to the context for the three references above

The environment of the CRM provides the necessary conditions for maturation and preclinical development
Twelve patents related to inventions underlying the development or improvement of innovative therapies were produced since 2017, including two that are already licensed. The scientific projects of the teams benefit from numerous interactions with private companies (Sanofi, Servier, Sarepta, Pfizer, Biogen). Partnerships with industry have significantly increased to become outstanding. Two CIFRE doctoral fellowships were obtained with Sanofi and Servier. Collaborative projects have been carried out for drug design and synthesis, co-developments with the teams have been carried out with Benitec Biopharma, Pfizer, Sarepta, Biogen, Ahead Therapeutics, or Shire®. Several services contracts were signed and 6 clinical trials were funded by private pharmaceutical companies, such as the Phase II/III for the treatment of the Inclusion Body Myositis. The interaction with the society is excellent with numerous presentations for college and high school students, as well as strong interactions with several patient associations.

Weaknesses and risks linked to the context for the three references above

None

ANALYSIS OF THE UNIT'S TRAJECTORY

The CRM plan for the next five-year period is to strengthen their research in the continuity of their current project and future activity to address new challenges and achieve breakthroughs in their two primary areas of activity:

1) understanding the basic biology of muscle within its normal and pathological environment,
2) and identifying dysregulated pathways or targets for innovative therapeutic developments (including small molecules/repurposing drugs and/or cell and gene therapies). Team 10 has been closed, which will give the opportunity to recruit a new team.

The future project aims at confirming the CRM as a key player in the French Myology landscape. Future research activities will be included in three major themes encompassing signal transduction from membrane to nucleus, RNA/protein homeostasis to cell function and autoimmune/inflammatory response.
Development of therapeutic approaches will build up on the proof of concept already established (RNA-based, gene therapies, cell-based therapy, drug repositioning). Combinatorial approaches will also be envisaged for complex neuromuscular diseases or to improve efficacy of current therapies. The clinical environment within the Pitié-Salpêtrière hospital and the Institute of Myology, and the integration of clinicians within CRM teams when they are not team leaders facilitate translation and integration of basic research with clinical research activities and also fosters back translation from bedside to bench to develop new areas of research. This last action is all the more realistic given the amplification of clinical research within the dedicated clinical departments and the Institute of Myology with establishment of registers and databases of patients by neuromuscular pathology, biobanking and the growing number of clinical trials. The CRM plans an increase during the next mandate of the implication of clinicians in the research teams.
The gathering of all CRM teams in the same building should be effective in 2025. The reunification of the CRM teams will involve a budget of more than 4 million euros mainly provided by SU for the renovation of the premices that will start in 2024.
The strategy of the CRM to reach its objectives is adapted and considers both scientific and management aspects, as well as the necessity to further develop contacts with industry and international visibility. The current deputy director will be director of the CRM and co-leader of a team, but will not have any other official function outside the Centre to avoid any possible conflict. This change is unanimously welcomed by the members of the CRM at the level of group leaders, researchers, as well as administrative and technical staff. In close interaction with the chief administrative officer, a direction office will be set up to facilitate both the necessary interactions with the academic bodies and the management of the CRM with the help of a steering committee composed of all team leaders and the direction to ensure a fluid circulation of all ideas and propositions, and take the decisions necessary to ensure a proper functioning of the CRM. Strategic issues, scientific orientations, organisation and internal life will be discussed in this committee.
Although discussions are still ongoing between the governing bodies, the evolution of AIM into a foundation of Myology with dedicated buildings could be a good opportunity for the CRM to increase its perimeter and visibility in the future. However, changes linked to the launching of the myology foundation will mostly concern the N+1 period (2030–2034) since it will probably only impact, if at all, the last years of the coming period.

RECOMMENDATIONS TO THE UNIT

Recommendations regarding the Evaluation Area 1: Profile, Resources and Organisation of the Unit

- Although significant, with a total of more than 1 million euros, European funds remain modest in the total budget of the CRM and could be further increased.
- The process related to the reunification of CRM in one building has been started in 2023. The sooner it is finalised, the better il will be.
- Administrative staff should be further increased to provide better support to the young researchers and technical staff.
- The website of the research teams should be updated.
- MyoBim (the bioinformatics platform) should be developed.
- The intranet should be finalised.
- Given the heavy workload, one or two deputy directors should be identified.
- The future director has initiated discussions with the DR6 to ameliorate communication and increase efficacy. This effort should be continued to ameliorate a situation deleterious for the CRM, both for contracts management and young researchers/students recruitment.
- Collaborations between teams have significantly increased over the period. This tendency should be strengthened. Funding of internal calls dedicated to collaborative projects would help to increase this tendency.
- Translational research requires an increasing number of skills and expertise that can hardly be mastered within a single team. The CRM should ensure that skills and cutting-edge techniques developed within each team will benefit all teams, creating a unique toolbox and knowledge basis for the CRM as a whole.
- The use of English for scientific communication is highly recommended.

Recommendations regarding the Evaluation Area 2: Attractiveness

The CRM should strive to increase the recruitment of postdocs
The CRM should take the opportunity of team 10 closing to launch an open call to recruit a new team. Offering a package could be possible and would increase the attractiveness of the position.
The involvement of CRM members as coordinators of international programs, especially EU programs, should be improved.

Recommendations regarding Evaluation Area 3: Scientific Production

The CRM has started to increase its standards of publication towards excellent journals. This tendency should be pursued.
Although the CRM has established international collaboration, it is recommended that the different teams further strive for more national and international collaborations

Recommendations regarding Evaluation Area 4: Contribution of Research Activities to Society

The CRM should strive to enhance its connexions with teaching, which are currently limited. Sorbonne University has just opened a junior professor position for the CRM, which is a good start.
The CRM teams should keep in developing partnership with industry, which will be instrumental to develop new treatments and clinical trials.

TEAM-BY-TEAM OR THEME ASSESSMENT

Team 1: Myomatrix & Myonucleus-related diseases: Genetics & Pathophysiology

Name of the supervisor: Gisèle BONNE

THEMES OF THE TEAM

The subject area of the team includes clinico-genetic investigations of neuromuscular disorders (NMD) and pathophysiology and therapy of striated muscle laminopathies and ECM-related disorders. The three main axes of the team are:

1) definition of the genetic and clinical spectrum of these NMDs,
2) investigation of the consequences of genetic mutations,
3) and development of therapies for these disorders.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

As recommended, the team has introduced a significant number of translational models and has established several international collaborations. It is still recommended to increase the number of large European or International grants. It is recommended to get last-author publication in high-impact journals.
As recommended, several collaborations within the CRC or with international partners with other thematic topics are mentioned in every project of the five-year objectives. It was asked to pay attention to the number of FTE in the subgroups and HDR in the whole team. The number of FTE will be reduced from 8 to 6.3 because of the departure of one PU-PH and one CCA. It is not possible to know exactly the number of FTE per subgroup, and the number of HDR will also be reduced from three to two in 2025, because of the departure of the PU-PH. It was recommended to keep a balance at the sex ratio. For the next mandate, only one out of eleven employees is a man.
It was recommended to involve more clinicians and University professors interested in different aspects of the diseases. No particular emphasis was put on this, but the team's experience together with the established collaborations should provide a sufficient level of expertise.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	1
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	2
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	10
Sous-total personnels permanents en activité	**14**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	2
Post-doctorants	2
Doctorants	1
Sous-total personnels non permanents en activité	**5**
Total personnel	**19**

EVALUATION

Overall assessment of the team

The team attractiveness is excellent (co-PI for 2 EU grants, coordinator 1 ANR; national/international meeting organisations, two basic and clinical European and international networks on NMD); however, the number of external funding as leader could be increased.
The productivity is very good to excellent with 80 original papers (17 in leading positions) in journals such as Circulation, Antioxidant, Brain, … but the number of last-authorship publications could be increased.
The dissemination to the general public is very good to excellent.

Strengths and possibilities linked to the context

The team published 80 original papers (17 first, co-first, last or co-last author) and 25 reviews, with the following highlights:

1) Development of a risk prediction score for ventricular tachyarrhythmias in laminopathies (Circulation 2019), 1st author from the team.
2) Characterisation of *INPP5K* as a new NMD gene (Brain 2021), involving human samples and test of therapies in zebrafish.
3) Efficacy of antioxidant treatment in a mouse model of LAMA2-RD (Antioxidants 2020), last author from the Lund University. The other publications represent well the subject area of the team and their collaborations within the CRM and at the international level.

The team leader and senior scientists were invited to 43 national/international meetings. They are involved in several basic and clinical European and International networks on NMD, including the coordination of the Filnemus network, treasurer of WMS, and past presidency of the SFM. The team contributed to the organisation of national (10) and international (16) meetings. The team leader was nominated by the Research Ministry in 2022 as the representative of the French rare disease community for the preparation of the forthcoming Rare Diseases Partnership for Horizon Europe 2030.

The total budget was 2,246 kE in 2017–2022, including 990 kE in 2022 (75% salaries and 25% running costs) funded by AIM (35%), Inserm (24%) and external funding (41%). This includes two European grants (H2020- 2018–2023, 358 kE, co-PI; ERA-CVD 2017–2022; 215 kE, co-PI), one ANR (2019–2023, 36 kE, coordinator), one Filnimus (2021-2022, 10 kE, co-PI), and five international grants as co-PI (Cure-CMD, MDA, MD-UK, ended or will end in December 2023, total 291 kE).

No novel recruitment in 2017–2022, but one promotion to Research Project Leader (AIM). There were five postdocs, incl. one Spanish, one Portuguese and one Japanese; Two are still active in the team. There were four students, three received their PhD in 2017 or 2018. One PhD has five publications, incl. one as 1st author, another one has six publications, incl. One as 1st author, and the last one has one publication as 1st author. Currently, the team has one doctoral candidate (SU). There was one CIFRE grant for a PhD student (2015–2018).

The team is well involved in the society and the public, incl. actions during the Fête de la Science, the Téléthon, 'Journées des Familles' with direct interactions with patients and their families, participation in the '1000 researchers in school' action as well as Declics initiative, where they meet pupils in schools and promote research to the youngest public.

Weaknesses and risks linked to the context

Currently, there are two postdocs, one recruited in 2019 and one in 2021 and one PhD candidate, who started in 2022. This number is relatively low to meet their project expectations.
One of the team leaders should reach more international leadership visibility, including last authorship's publications.

Analysis of the team's trajectory

The team's name will be 'Translational research on muscle extracellular matrix and nucleus (TREASURE)', composed of two team leaders, three subgroups, a total of eleven members, incl. 6.3 FTE (2 Inserm — 3.3 AIM – 1 APHP).
The proposed five-year strategy will follow the previous achievements of the team with a strong focus on translational research on muscle extracellular matrix and nucleus.

The team is smaller, but still has three project leaders. One senior team leader will coordinate the transversal activities of the team and interactions with the clinicians, while the other team leader will lead the ECM-related projects and the other senior scientist will supervise the laminopathy-related projects. Several grants are pending, such as to the Leducq Foundation, ANR, EU Horizon Europe-Rare disease, MDA, …). The projects will be divided as follows:

1) Clinico-genetic investigations of NMDs. The team will pursue the evaluation of unsolved NMD cases with multi-omics and AI approaches. The Treatabolome database initiated by the team leader, will be expanded and disseminated. Collaborations with clinicians and other scientists will continue over national and international networks. For this project, no new challenges are expected.
2) Striated muscle laminopathies. The group aims to identify new gene/variant modifiers associated with variable clinical phenotype and will pursue its research activities on the pathophysiology and test of therapeutic options. One new PhD student started on this project in October 2022. For this project, they have new challenges: i) the use of myo-converted fibroblast model for RNAseq and ChIPseq, ii) interactome of delK32 lamin mice with BioID technology, iii) the hypothesis (likely based on the recent report of Sastourné-Arrey et al., Nat Comm 2023) that the lack or immaturity of adipose tissue reduce MSC number and ability to invade skeletal muscles in mutant mice; iv) new strategies for gene therapy.
3) ECM-related disorders. The group will evaluate their molecular basis and pathophysiology, therapeutic strategies for nonsense mutations and pathophysiology and therapy of LAMA2-RD. Main challenges are the establishment of cell culture conditions to model fibrosis for screening anti-fibrotic molecules, obtention of hiPSC-model of LAMA2-RD and test of the ACE-tRNA strategy to correct premature stop codons.

The team will continue collaborations within the CRM and with international scientists. The team environment will allow access to patient cohorts via the NMD reference centre (lead by one of the team members) and the Filnemus and Oscar networks. Furthermore, all technical facilities of the CRM or SU will be essential for the team's projects (cell immortalisation, AAV production, imaging, molecular biology, animal care, P3S post genomic).

RECOMMENDATIONS TO THE TEAM

The current number of postdocs (2) and PhD candidates (1) is too low to reach the project expectations. It is recommended to recruit more PhD candidates and postdocs (at least 1 of each per group project).

It is also important to consider more last authorships for the three PIs in the future, specifically for one of the senior scientists, who did not publish as first or last author in 2017–2022, maybe due to the sabbatical.
Publications in high impact journals should remain the team target.

Despite the annual support of AIM, most external grant fundings will be finished by the end of 2023, except for two that will end in 2024 and 2025 for one of the team leaders. It is important to consider new applications very soon.

Finally, the committee is encouraging the development of projects that will enhance the thematic cohesiveness of the team.

Team 2: Muscle cell organisation and therapy of dominant centronuclear myopathy

Name of the supervisor: Marc BITOUN

THEMES OF THE TEAM

The team works on the understanding of muscle biology processes in order to decipher the pathophysiological mechanism of the dominant centronuclear myopathy (CNM) caused by DNM2 mutations. Additionally, they are dedicated to pioneering novel therapeutic strategies for CNM.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Following the previous recommendations, the team hired a clinician (0.5 FTE) to foster translational studies. The number of PhD students is in line with the recommendations while few postdocs were recruited. The scientific output was increased with several publications in high-impact journals. The team set up numerous national but few international collaborations. Following the recent advances in promising therapeutic developments, and following the recommendations, the team is about to launch collaborative contracts with private partners.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	1
Directeurs de recherche et assimilés	3
Chargés de recherche et assimilés	3
Personnels d'appui à la recherche	1
Sous-total personnels permanents en activité	**8**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	2
Post-doctorants	1
Doctorants	3
Sous-total personnels non permanents en activité	**6**
Total personnels	**14**

EVALUATION

Overall assessment of the team

The attractiveness of the team is excellent, with members invited to national and international meetings and the size of the team has more than doubled since its creation in 2014 (from 6 to 15). The team has consistently secured national funding (as coordinator of 2/5 ANR, 2 SU Emergence and French associations other than AIM). However, the international funding and the recruitment of postdoctoral fellows could be increased.

The scientific production is excellent to outstanding (57 original papers, 17 in leading position in EMBO Mol Med, Sc rep,..) , international collaborations, and state-of-the-art innovations in cell imaging.

The valorisation is very good to excellent, including two submitted patents on the allele-specific silencing therapy for CNM (one approved, one pending).

Strengths and possibilities linked to the context

Exterbal funding obtained by the team was 2.4 million € in 2017–2022. The team budget was 1.2 million € for 2023 (75% salaries and 25% running costs) funded by INSERM (57%, including external grants), AIM (35%), and Sorbonne University (7%). The team does not have European grants but received ten National Grants: five ANR

grants (€1.1 million; 2 as Coordinator), one Inserm Transfert grant (174 k€, Coordinator), two Sorbonne University Emergence grants (123 k€, 2 as Coordinator), and one Bettencourt Foundation grant (70 k€, Partner), and one PACS1 French association grant (58 k€, Coordinator), plus six PhD contracts (600 k€). The AIM-AFM finances the salaries of 4 permanent positions (3 researchers and 1 technician) as well as a part of the running costs of the team (around 100k€ per year).
During the last period, five PhD students completed their thesis, and three postdoctoral fellows were part of the team. One clinician was recruited in 2020 and three PhD students started their thesis in 2022 while only one postdoctoral fellow is part of the team.

Since the last evaluation, the team members were co-authors in 57 original papers (17 co-first, last or co-last) and 6 reviews (6 first or last authors). Ten papers co-authored by at least one member of another CRM team and ten papers co-authored by members of the CRM internal platforms out of our 27 PDC articles.
Out of these, three achievements linked to high-profile journals could be underlined:

i) The development of versatile allele-specific siRNAs able to silence all the dominant DNM2 mutations was published (EMBO Mol Med 2018; Mol Ther Nuc Acids 2022), with the team leader as the last author;
ii) that muscle regeneration impairs transcription of therapeutic AAV transgenes (Sci Rep 2022);
iii) a major technological achievement with the development of a metal replica of unroofed cells analysed by transmission electron microscopy, allowing visualisation of the cytoplasmic face of the plasma membrane and the associated cytoskeleton at the nanoscale. This pioneering work has contributed to many international collaborations and publications in high-profile journals (11 listed here).

Students and postdoctoral fellows are well integrated in publications, with an average of two publications for students and between one and three for postdoctoral fellows.
Around 95% of the team's articles from 2017 to 2022 are in open access. The plan is to expand the sharing of methods and raw results.
The team is involved in the society through participation at the 'Journée des familles' organised by AFM-Telethon, the 'Fête de la Science' event, and the '1000 researchers in school' action. One permanent member of the team co-organised the 'Festival Science, culture et société' at Sorbonne Université (Paris, 2021) and co-organises each year dialogue between researchers and High School Students (Declics). Two patents have been filed.

Weaknesses and risks linked to the context

Although the Team receives consistent financial support from ANR and various French associations (including AFM-AIM), it lacked international funding and contracts with private companies until 2022. Additionally, the team should envision the need for additional postdoctoral fellows to effectively accomplish the project's objectives. Also, despite the overarching theme of centronuclear myopathy, the projects pursued by the team exhibit a significant degree of diversity, which covers a bigger area of research but could weaken the consistency of the team. Furthermore, it is advisable for the team to reduce publishing in the MDPI journals (e.g. *Cells*), as some grant agencies may view this publisher as questionable in terms of quality and credibility.

Analysis of the team's trajectory

The proposed five-year strategy will follow the previous Team achievements with a strong focus on pathophysiology and therapy of CNM (led by the team leader) and the role of the endocytosis machinery in muscle mechanotransduction (led by a permanent team member).
The Team will be headed by two leaders, who have been working together since 2009. This follows the evolution of one member to the leadership of the Team while alleviating the workload from the current leader, whose responsibilities extend beyond lab management (coordinator of platforms, University Research Commissions and INSERM CSS3 commission).
Two main axes will be followed:

1) Mechanobiology in healthy and pathologic muscles. The team will determine the role of clathrin plaques and the endocytosis machinery as platforms for YAP/TAZ mechano-signalling. The impaired tissue-specific alternative splicing of clathrin in DM1 will be investigated, using skipping and inducing mis-spliced exons on iPSC derived neurons and myotubes from patients. Mechanotransduction will be studied as well in A-type laminopathies with a focus on the force-mediated regulation of nuclear stiffness and deformation, chromatin/histone modifications, and genetic programs in muscle cells (RNAseq with Atacseq on myotubes subjected to cycling stretch).
2) Development of therapeutic approaches to dominant centronuclear myopathy using allele-specific silencing therapy, for which the team has strong expertise. The objective is to determine the best AAV vectors (serotype, dose and promoter) for systemic injection. Such an approach will also be developed for other neuromuscular diseases like PACS1 syndrome. In parallel a high throughput will be done on cells from DNM2-CNM patients in collaboration with Istem (Evry, FR) and financed by AFM-Telethon. Efforts will be put into improving the AAV transduction efficacy in diseased muscles with a focus on trafficking and endo-lysosomal pathways.

The team is requesting additional technical staff. Since permanent positions are not possible (by INSERM, Sorbonne University or AIM), recruitment will be based on external funding.

RECOMMENDATIONS TO THE TEAM

- It is expected by the team to have more than one postdoctoral fellow.
- Despite the general theme of centronuclear myopathy, the projects are diverse and the overlap between the two groups is limited. More overlapping projects as proposed in the future project of the team would better justify the team's structure with two groups (instead of 2 separate teams).
- Invest in high-quality projects and expand international collaborations to acquire international funding.
- Publications in high-impact journals should remain the Team target.
- Limit the publications in MDPI which might be considered by several grant agencies as questionable in terms of quality

Team 3: Cellular and molecular orchestration in muscle regeneration, ageing and diseases

Name of the supervisor: Capucine TROLLET

THEMES OF THE TEAM

The team works on molecular and cellular actors involved in human muscle regeneration. Studies are performed in the context of muscle ageing and diseases, with a particular focus on a rare disease called oculopharyngeal muscular dystrophy (OPMD). The objectives are to understand cell communication during ageing, fibrosis and regeneration, and to develop therapeutic strategies relevant to muscle ageing, fibrosis and pathological conditions (OPMD).

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team continued to publish well in high-quality journals both as FLC authors and in collaborations. The team followed the recommendation and increased its visibility towards a large public through Twitter (now X) and LinkedIn accounts created by several members, as well as via interviews and press articles.
The team managed to recruit one additional permanent staff member. It does not have yet international grants as PI. The topics of research remain rather broad (ageing, fibrosis and various pathologies).

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	2
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	4
Sous-total personnels permanents en activité	**8**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	5
Post-doctorants	1
Doctorants	3
Sous-total personnels non permanents en activité	**9**
Total personnels	**17**

EVALUATION

Overall assessment of the team

The team has an excellent national and international reputation in human muscle regeneration and disease, with a strong expertise in OPMD.

The scientific outputs are very good to excellent: 67 papers with eighteen in leading position in speciality journals (Acta Neuropath 2022, J Cach Sarcop Muscle 2022,..).
The budget is excellent, secured through a variety of financial supports (Équipe labélisée FRM, fondation de l'Avenir..), including 4 private companies. The research topics are numerous, centered around muscle regeneration in health and disease/ageing, and in understanding the pathophysiology of OPMD, and treatment development.

Attractiveness is excellent. The team co-leaders are regularly invited to give presentations at national and international meetings. Five theses were defended since 2017. The team has few postdocs.

Valorization is excellent, with three patents and three industrial contracts.

Strengths and possibilities linked to the context

The team has an excellent national and international reputation in human muscle regeneration and disease, with a strong expertise in OPMD. Strengths of the team include work with human material, development of a xenograft model of human biopsies in immunodeficient mice and continuous updating of the MyoLine platform. The budget 2017–2022 was of €1.8 million, plus 200 k€ for doctoral contracts and more than €1.6 million from the AIM, which allowed recruiting three postdocs, 6 PhD students and eight research assistants/associates. Fifteen grants were obtained by the leaders: Équipe labélisée FRM (271 k€), Grand Donateur Myomessage 150 k€, fondation de l'Avenir 25 k€…. , most of them as coordinators. Three grants (447 k€) were from private companies (Kaneq Bioscience100 k€, Bioblast 68 k€, Benitec Biopharma 279 k€).
The team co-leaders are regularly invited to give presentations at national and international meetings. The PhD and postdocs actively participate in meetings. During the last period, five students completed their PhD and three postdoctoral fellows joined the team, one is foreseen obtaining a permanent INSERM position. Currently, four PhDs are in the laboratory, and a Brazilian postdoc joined the team this spring. A co-leader was promoted DR CNRS 1st class and the other DR2 INSERM. One staff member was promoted project manager AIM and two AIM research associates were recruited. The team is the French partner of FIOCRUZ in Brazil which allows PhD and postdocs exchange.

The team published 67 papers during the last period, including eighteen as FLC authors, and eight as last authors for the team leaders. The publications are in good to high-impact journals. One can highlight 1) a study on the beneficial impact of a dual therapy based on AAV-delivery of RNA interference to knockdown gene expression together with the re-expression of a wild-type version of the mutated gene (PABPN1) in the case of OPMD (Nat Comm, 2017), 2) an extensive analysis of the PABPN1 aggregates revealed the presence of unidentified proteins (BiP, RPL24 and p62). The team used an innovative approach of xenograft whereby a human OPMD muscle sample is transplanted in immunodeficient mice. Following the fate of the PABPN1 aggregates during muscle regeneration led to a proposed mechanistic view explaining the late onset and specificity of the disease (Acta Neuropath 2022), 3) to unravel the key functions of FAPs in fibrotic muscles, during ageing and in diseased conditions (OPMD), and discover ET1 as a new promoter of fibrosis, stimulating ECM deposition by the FAPs. ET1 receptor is proposed as a new therapeutic tool (J Cach Sarcop Muscle 2022). Three patents on OPMD and fibrosis treatment were obtained, and one is currently submitted, highlighting the translational side of the team's research. PhD students and postdoctoral fellows have a good to very good publication record.
The team has three contracts with private companies, as leader, for therapy development and a collaborative contract with Sanofi (50 k€) for developing biomarkers for inflammatory myopathies. The team maintains contact with patient associations and actively participates in the Téléthon, '1000 researchers in school', and others. One of the team Leaders participated in a MOOC that will be launched in 2023. The team is active on social networks, CRM websites, gave interviews and wrote press articles.

Weaknesses and risks linked to the context

The number of permanent staff members is low compared to the projects planned by the team. The team aims to compare various pathologies to reveal their common and divergent physiopathological traits. This relevant approach contains a risk of dispersion and requires important resources that might be lacking in the team. The postdoctoral fellows are few and there is no indication of future recruitments (besides the Brazilian postdoc who joined the team this year). The role and implication of the Emeritus member of the team is not clear.
The link between OPMD and ageing is not obvious
The lack of European/international funding may be an issue that fosters the difficulty to recruit at the postdoctoral level. The distribution of tasks between co-leaders is not clear.

Analysis of the team's trajectory

In the next five years, the team will pursue its work on the cross-talk between cell types during muscle regeneration, on muscle fibrosis and on the development of innovative therapeutic approaches for rare diseases such as OPMD. Two main axes of research will be followed:
Understanding the cell communication during muscle regeneration. The team will determine the impact of selected myokines on muscle regeneration in various pathological conditions and during ageing. The common/diverse processes of fibrosis will be addressed in various pathological conditions, and the role of FAPs as key players of ECM deposition will be studied in depth through proteomic, RNAseq and mass cytometry approaches and in collaboration with the team of Dre Bonne for congenital muscular dystrophies.
Development of therapeutic approaches, with a strong focus on OPMD, for which the team has a strong international reputation. The role and the regulation of PABPN1 (mutated in OPMD), which is found in nuclear aggregates will be investigated. More generally, the common and diverse mechanisms of protein aggregates in various pathological and ageing conditions will be explored in human tissues, with the aim of developing specific therapeutic approaches for various muscle conditions. In line, the team developed pharmacological approaches to target protein aggregates in collaboration with several groups in France and obtained financial support from SATT OUEST to optimise anti-prion molecules. In addition, the team is currently working with Benitec

Biopharma on phase I/II clinical trial on OPMD using a knockdown/gene replacement strategy developed by the team.

RECOMMENDATIONS TO THE TEAM

The team needs to recruit more permanent positions, the ratio between permanent and Emerite positions is not optimal. Only two FTE positions are full-time.
The Team should recruit postdoctoral fellows to impulse dynamism.
The involvement of technical staff is not completely clear, and their roles should be more clearly defined.
Several projects aim to consider different diseases/ageing common or divergent characteristics. This appears a pertinent and valuable question to ask but maybe there are too many diseases needed to be investigated for the size of the team.
The research plan for the next years is very consistent but might be too broad for the team size, especially since the link between OPMD and ageing is not obvious.

Team 4: Repeat Expansions & Myotonic Dystrophies

Name of the supervisor: Denis FURLING & Geneviève GOURDON

THEMES OF THE TEAM

This team is focused on Myotonic Dystrophy type 1 (DM1), the genetic, neuro-muscular disease caused by expansion of CTG repeats. It aims to understand the underlying mechanisms and the associated pathophysiology and to develop therapeutic strategies. The team combine both molecular/cellular and clinical aspects of the disease.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team published well in high-quality journals both as FLC authors (total 38 papers, including Nat Comm, Nat Biomed Engineering, Brain, Cell Rep) and in collaborations. The team followed the recommendations to increase the publications in journals with high visibility and to host visiting scientists from other countries.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	1
Maîtres de conférences et assimilés	1
Directeurs de recherche et assimilés	2
Chargés de recherche et assimilés	5
Personnels d'appui à la recherche	3
Sous-total personnels permanents en activité	**12**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	6
Post-doctorants	3
Doctorants	4
Sous-total personnels non permanents en activité	**13**
Total personnels	**25**

EVALUATION

Overall assessment of the team

The team is recognised as an international leader for its work on myotonic dystrophy type 1.
The scientific production ranges from excellent to outstanding with 38 papers as PDC in high-profile journals such as Nat Comm, Nat Biomed Eng, JCI, Cell Rep…

Attractiveness is outstanding. All members are producing very well, actively participated in national and international meetings and have received international and national prizes, including the Steinert Award for Excellence in Myotonic Dystrophy, from the scientific board of the 12th International Dystrophia Myotonica Consortium. The budget is secured through different financial support, including eight private companies (Pfizer, pepGen, …) and foundations (AFM, FRM, ..).

Valorisation is outstanding, with eight contracts with industry (Pfizer, Pepgen …).

Strengths and possibilities linked to the context

The team is composed of twelve permanent and thirteen non-permanent positions working on one specific topic, the DM1, that is a major strength in terms of scientific production and contribution to this field. The research topics are focused on understanding the pathomechanism of DM1 and on treatment development of the disease. Previously the team was focused on the generation of mouse models of the disease and solving the problem of molecular bases of DM1. More recently the team has been significantly strengthened by the joining

of a clinician, one of the team leader, responsible for, among other things, the largest registry of DM patients and who is involved in several clinical trials. Indeed, the number of publications (38 as FLC and 69 as collaborators) in journals such as Nat Comm, Nat Biomed Eng, JCI, Cell Rep.
Two patents, one license with Pepgen and 21 licenses for the mouse developed in house confirm the very good productivity of the team. The quality of the research is also highlighted by prizes that PI, postdocs and PhD students received at national and international conferences.
The team obtained 25 contracts (8 as collaborators): as PI, in international grant (Marigold Canada, 300k€); two ANR-PRC (TheraDM and ASTROMYOD, €760 total; one ANR JCJC MOTORDM (240k€); with eight private companies (Pfizer 800k€; Pepgen 240k€, …) for therapy development that confirms the leadership in DM field; and from 7 foundations (AFM, 446k€; FRM 141k€, …– The budget is good to support the research of the team and is estimated around 2 million euro in which 14% is coming from industries and 15% from national and international grants.

Weaknesses and risks linked to the context

Due to the size of the team, the possibility to recognise the work of the different scientists and especially of the youngest ones may be problematic. The funding is excellent (~ 700 k€ running costs per year) but still weak in terms of having international grants especially significant grants from EU as a leading researchers. Now 30% of the budget is spent for running costs. This percentage could be higher as the research team is really big (25 positions). The number of postdocs should be implemented in particular the ones coming from foreign countries. The low level of European/international funding may also contribute to the low number of international postdocs.

Analysis of the team's trajectory

In the next five years, the team will pursue its work on three major axes related to 1) CTG repeat expansion mechanisms, 2) pathophysiological insights and 3) therapeutic interventions. To reach these goals the team will develop several tools including mouse models and iPSCs from DM1 and DM2 patients. The team also aims to move and explore DM2. The objective that the team wants to address are focused and clear. The experimental approaches of each major aim are well designed. The therapeutic development will attract the industry partnership and strengthen the already existing ones.

RECOMMENDATIONS TO THE TEAM

The team should maintain the effort in publishing on highly quality journals and should implement the successful rate of international grants. International environment should be improved by having more visiting scientists and postdocs from abroad. The recognition in terms of leadership of the young scientists in the team should be taken into account. Visibility of all team members in terms of authorship in major publications is not equal. Stronger collaboration between team members representing molecular and clinical aspects of the myotonic dystrophy can significantly strengthen future projects.

Team 5: Muscle mass and function maintenance and optimisation of AAV-based gene therapies

Name of the supervisor: France PIETRI-ROUXEL

THEMES OF THE TEAM

This team focused on developing innovative approaches to improve the treatment of Duchenne Muscular Dystrophy (DMD) and some other neuromuscular diseases.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The team published well, including high-quality journals as FLC authors (5 papers including one published in Sci. Transl. Med). The team followed the recommendations to increase the publications in journals with high visibility but still mostly in collaborations (total 18 papers including two published as co-authors in EMBO Molecular Medicine). It recruited five new PhD students but did not obtain international grants as PI or is not a part of joint European projects. The team got, however, larger funding from industry. The topics of research remain rather broad. There is still a gender imbalance while the team leader has increased international visibility and profile. The scientific strategy has been revised and is more focused and includes some cutting-edge technologies that would add values for the discovery of novel therapeutic approaches.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	2
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	2
Sous-total personnels permanents en activité	**5**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	1
Post-doctorants	0
Doctorants	3
Sous-total personnels non permanents en activité	**4**
Total personnels	**9**

EVALUATION

Overall assessment of the team

The team is well recognised for its work on AAV virus, their therapeutic application in Duchenne muscular dystrophy (DMD) and on the recent discovery on GDF5 as a positive modulator of muscle mass.

The scientific production is very good to excellent with eighteen papers, thirteen in collaboration. The team has already produced publication in high-ranked journal with first/last authorship (Science Translational Medicine) and is encouraged to increase this number.

The attractiveness is very good in terms of international visibility and with three PhD under supervision but no postdoc as of December 2022. All members produced well, actively participated in national and international meetings. One PhD candidate received a prize at an international meeting. The budget is secured through financial supports mainly from private companies (SAREPTA) and AFM.

The valorisation is excellent in terms of patents (2) and collaboration with industry (Servier CIFRE).

Strengths and possibilities linked to the context

The team is composed of five permanent and four non-permanent positions working on one main topic that is related to GDF5, its regulation and its potential implication as therapeutic target for sarcopenia, DMD and ALS. The focus on GDF5, which was discovered to play a beneficial role on muscle mass by the team, is a major strength that may be translated into therapeutic application. Two patents have been generated that cover the application of GDF5 administration as therapy of sarcopenia and DMD. These patents underlined the translational approach of the team that is further strengthened by the obtention of contracts with private companies for therapy development.
The budget is good to support the research of the team and is estimated around 1.3 M€ in a period of 2017–2022, including ~60% of running costs. Funding obtained, as PI, include: one major industrial contract (Sarepta Therapeutics (2017, 758kE) and a strategic project AFM (STRONG 488 k€).
The team obtained a CRCN-INSERM recruitment grant 30 K€ and a CIFRE fellowship (Servier CIFRE PhD support 48 k€)

Weaknesses and risks linked to the context

The number of permanent staff members is low compared to the projects planned by the team. The team aims to compare GDF5 treatment in various pathologies to reveal the beneficial effect. This relevant approach contains a risk of dispersion and requires important resources that might be lacking in the team. There is a lack of experience in cutting-edge technologies, such as omics, spatial omics, multiomics at single cell but also organoids, that would be critical for the future projects. The funding is good but weak in terms of having international grants especially from the EU. There are no postdocs in the team and this is a limiting factor for the success of the five different aims/sub aims. The number of publications in international peer-reviewed journals during the last five years in which the team is FLC is low. This is partially a consequence of the work performed on two patents, which limited the possibility to publish the results.

Analysis of the team's trajectory

In the next five years, the team will aim at understanding the role of the CaVβ 1/GDF5 pathway in counteracting loss of muscle mass and in optimising therapeutic strategies for sarcopenia, DMD and ALS. The team has already developed a synthetic molecule that acts as mimetic of GDF5 and have extended half-life. This molecule will be tested in sarcopenia and this work will be sponsored by Merck Fondation (614 k€). Similar approach will be applied to DMD by treating the rat R-DMDdel52 with synthetic GDF5 and to ALS by overexpressing GDF5 in SOD1G93A ALS mouse model. In the DMD subaims the team will take advantage of a combine snRNAseq – Spatial Transcriptomic to identify which cell populations are responding to GFD5 and how the cellular crosstalk within the regenerating niche is modulated by the treatment. For the first aim related to the insights of CaVβ 1/GDF5 regulation, the team explore the role of Mbnl proteins in exon splicing for CaVβ 1D and CaVβ 1E expression. In addition, they also aim to decipher the role of CaVβ 1-E in DM1 pathophysiology.
The objectives are broad (for the team size especially because there are no postdocs with established experience in the different diseases and experimental approaches. The experimental plan is sufficiently described but it is not clear which experiments will be prioritised. The therapeutic development has already attracted the industry partnership, and this is already a major achievement for the translation aspect of the project.

RECOMMENDATIONS TO THE TEAM

The team has generated two patents and another one is in preparation, but the publication track record should be improved. The team should put an effort in increasing the publications with particular attention in publishing on high impact journals, especially for papers with major contribution of team members (first/last authorship). Improving the publication track record will also enhance international visibility and will help to increase the successful rate of national and international grants. Working on DM1, DMD, ALS and ageing sarcopenia requires recruitment of postdocs for being successful. In case that the team budget does not allow a successful recruitment, the team should consider to be more focused and prioritise the diseases that aim to be studied.

Team 6: Epigenetics and biotherapies of motoneuron disorders

Name of the supervisor: Piera SMERIGLIO

THEMES OF THE TEAM

The team aims at the understanding of the molecular mechanisms underlying both the neuronal and musculoskeletal defects in motor neuron disorders (MND) and finding efficient therapeutic strategies for Spinal Muscular Atrophy (SMA) and Amyotrophic Lateral Sclerosis (ALS).

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The recommendations made to the former leaders of the team (requirements for a clear joint strategy and for increasing their international profile) are now obsolete since they left the CRM in 2021. The requirement on acquiring larger funding was pursued, including high funding from Industry in 2021 and from national grants in 2022.
Recommendations to recruit more PhD students and to increase the male/female team member ratio were only partially followed, with 2 PhD students.
The recommendation on joint funding was followed with a new AFM grant in 2022 with an Italian group, as well as collaborative grants from ANR PRC and ARLSA.
The requirements to separate the strategy in translational and pathomechanism parts and to exploit the added value of team members have been followed.
Recommendations to reduce the sidetracked projects on pathophysiology (minor pathways) and to start a gene editing therapy are not discussed.
The recommendation to consider if working on C9orf72 antisense strategy is wise was proven by their patent licensing to an American company.
The recommendation to strengthen the collaborations with clinicians has been followed and the team can enroll patients from the local SMA reference centre for future clinical studies.
The recommendation to look for innovative projects was pursued with the identification of multi-system involvement in SMA and thymus dysfunction in ALS.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	3
Sous-total personnels permanents en activité	4
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	4
Post-doctorants	4
Doctorants	2
Sous-total personnels non permanents en activité	10
Total personnels	14

EVALUATION

Overall assessment of the team

The team's name in 2017 was 'Biotherapies of Motor Neuron Disorders' and was led by two scientists until their departure from the CRM in 2021. The team leader is very young with an excellent international visibility on motoneuron disorders (NMDs). The team received grants (2ANR as PI), running until the end of 2024 and 4 fundings from the industry which confers excellent attractiveness.
Scientific production is good, with 34 papers, eight in leading positions in journals such as J Pers Med, Mol Ther. However, the young team leader who took over the management in 2022, just after being appointed at Inserm, already has many manuscripts in preparation.
Valorisation is excellent with two accepted patents and involvement of the team in national clinical trials.

Strengths and possibilities linked to the context

The current team leader was a postdoctoral fellow in this team since 2019 and took over the lead in 2021 and renamed the team to match the additional research direction, which leverages on the knowledge of epigenetic control to enhance therapeutic approaches for SMA. This is thus a very young team.
The team has partnerships with Brazil, USA & Italy, which help to attract postdocs and PhD students from these countries. The team leader has co-organised three meetings on MNDs in Italy and France. The team leader is also part of the steering committees of AIM and AFM-Téléthon to design the research strategic plan for the next five years.
Team leaders have been invited to eighteen national or international meetings and team members have participated in several meetings with a poster or an oral communication.
The budget was 6305 kE in 2017–2022, including 1082 kE in 2022, which is outstanding for a young team. This includes one European grant for PhD salary (Horizon 2020-MSCA, PI, 25 kE), two ANR grants (PI, 241 kE; co-PI, 58 kE), several grants with the industry, such as Chameleon Biosciences (PI, 195 kE), Sanofi (PIs, 1 500 kE), 3x Athena Cos (2x PI, 97 kE and 117 kE; PI, 82 kE), and several grants from Foundations, incl. Fondation de France (PI, 72 kE), Fondation Thierrry-Latran (PI, 150 kE), AFM-Téléthon (PI, 15 kE), Fondation Carrefour (PI, 150 kE).
The current team leader was recruited as CRNC Inserm in 2021. The team supervised four postdocs, one PhD student, four research assistants and one Master student.
The team published 34 papers, eight in leading positions in journals such as J Pers Med, Mol Ther, … and two international patents in 2017–2022. An additional Patent application is pending. It may look low, but several findings are under Embargo with Industry partnerships.
The team has strong collaborations with the industry and has continuous collaborations with patients and clinicians of the Neuromyology Department (directed by T Stojkovic, Team 1 member) for research of molecular biomarkers and therapeutic strategies for MNDs. The team contributes to the scientific community via uploading genomic data sets and bioinformatic pipeline scripts via GEO and R script repository, GitHub and Biopython bioinformatics for package archive.
The team is actively involved in the society during the annual AFM-Téléthon and ruffle fund-raising, during the Family Days where they meet patients and families, and finally to the Pint of Science initiative for public dissemination of science into local pubs. Furthermore, the team contributes to the dissemination of knowledge via teaching at the SU and Neuromuscular Research Center, and through the '1000 researchers in the school' program, website, Twitter and LinkedIn accounts.

Weaknesses and risks linked to the context

The team leader needs last-author publications.

Analysis of the team's trajectory

In 2025, the team will be composed of 3.73 FTE (1 Inserm – 4 AIM – 1 SU). They will integrate two new members, incl. the past CRC director (w/HDR) and one PH. Senior postdocs will lead their own projects.

The combination of the expertise of the team leader (epigenetics, neuromuscular development, tissue regeneration and bioengineering), of the project leaders (therapeutic vector development and bioinformatic pipelines), of research assistants (industrial-level AAV production and animal function analysis) and of the clinicians is recognised for translation of their findings.

The team leader planned to get the HDR and to support the application of one of the team members for a permanent researcher position.

The current grant fundings are running until the end of 2024 and 2025, including Industry partner. One of the team members received a Marie-Curie fellowship for three years in 2023.

The collaborations within the CRM and at the international levels are well defined, including their participation in the SMOB clinical trial.

The team will use a combination of state-of-the-art technologies, including multi-omics data feed the machine and learning networks to identify novel non-coding cis-regulatory regions underlying disease variants in motor neuron disease, convolutional neural network approach, and development of new AAV capsids for AAV-mediated therapy to cover a broader spectrum of MND.

RECOMMENDATIONS TO THE TEAM

A – Recommendations on scientific production and activities (criterion 1)

It is recommended to get new European grants to increase the team leader visibility.
It is required to get last authorship publications for the team leader. The current high impact publications were done in collaboration and led by Stanford university.

B – Recommendations on the team's organisation and life (criterion 2)

It is recommended that the team leader gets the HDR.
It is recommended to get more PhD candidates.
It is recommended to consider gender parity in the team in the future by recruiting male postdocs and PhD candidates.

C – Recommendations on scientific strategy and projects (criterion 3)

It is recommended to develop collaboration with the clinical reference centre for ALS and other motor neuron diseases and with the Filslan network ('Filière maladies rares SLA et autres maladies du neurone moteur').
It is recommended to consider communications in ALS-MND meetings as they develop highly competitive academic translational research with extremely promising results.

Team 7: Myasthenia Gravis: etiology, pathophysiological & therapeutic approaches

Name of the supervisor: Rozen LE PANSE

THEMES OF THE TEAM

The team has a unique expertise in the study of Myasthenia Gravis, being the only team in France entirely dedicated to this pathology. They take interest in deciphering the mechanisms involved in this pathology and explore therapeutic approaches.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

In agreement with the previous recommendations, the team has started to establish more connexions with other Teams in the institute. The team also implemented more cutting-edge technologies in their pipelines, in particular mass cytometry and single cell approaches.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	2
Chargés de recherche et assimilés	1
Personnels d'appui à la recherche	3
Sous-total personnels permanents en activité	**6**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	2
Post-doctorants	1
Doctorants	1
Sous-total personnels non permanents en activité	**4**
Total personnels	**10**

EVALUATION

Overall assessment of the team

This is the only team in France working on Myastenia Gravis, and this unique expertise is a major strength. The team displays an excellent research capacity, using state-of-the-art approaches to dissect Myestenia gravis, ranging from cellular approaches to therapies.
Scientific production: The publication record of this team is very good to excellent, with 25 papers including eighteen directly from the team in leading positions in journals of specialty (such as Annals of Neurology, Acta Neuropathologica, J Autoimmun, J Neuroinflammation).

The attractiveness of the team is excellent with one collaboration in a EU grant, many international collaborations. The team managed to secure 4 national grants (2 ANR as PI) and is involved as a partner in European initiatives.

The team is also engaged to a lesser extent in collaborations with industrial partners, allowing very good valorisation.

Strengths and possibilities linked to the context

The team is the only one in France to work on MG and is well recognised internationally. Since 2017, research projects are led by 4 researchers working closely together. The team has benefited from the arrival of a DR2 CNRS in 2018 and from the recruitment of a AIM CR in 2019.
The team takes part in international networks and has established International partnerships with Italy, Netherlands, Turkey, Greece and Belgium. The team leader was a member of the steering committee to organise the 14th MGFA International Conference on Myasthenia and related disorders in Miami 2022. Additionally, the Team participated to nineteen national or international as invited speakers. Speaker invitations and participated to several meetings through poster or oral communication.
The team's budget is very good to excellent and amounted to a total of 1,569 kE in the 2017–2022 period. This budget is broken down in European Grants (Era PerMed: collaborator, 260 kE), national grants (2 ANR-PRC as PI 692 kE, 1 as collaborator; SU Emergence.), Industrial grants (Ahead therapeutics – PI, 66kE) and five foundations-related fundings (4 AFM-Téléthon – PI, 332 kE, Agence Biomedecine – PI, 20kE)
During the priod, the Team recruited one DR2 CNRS and one permanent researcher (AIM). Finally, the Team provided supervision to two postdocs, 4 PhD candidates, two research assistants and 25 Master students. Those staff were gender-balanced.
The scientific objectives of this team are to understand the pathophysiological mechanisms of MG, and to elucidate the pathogenic events involved in the initiation and the chronicity of the disease, with the long-term goal to propose new therapies. The team published 25 papers whose eighteen directly from the team. Some papers have been published in excellent journals (Annals of Neurology, Acta Neuropathologica). Research has been focused on MG pathophysiology: epigenetic susceptibility, thymic inflammation, immunoregulation defect and role of anti AchR antibodies. They also developed new therapeutic targets: anti-IL-23 monoclonal antibody, Wnt/β-catenin pathway and liposome-based immunotherapy. The committee noted a marked effort towards collaborations inside and outside the institute, which is highly appreciated.
During the priod, the Team continuously collaborated with patients and clinicians of the Neuromyology Department (directed by T Stojkovic, Team 1 member) and Reanimation clinicians. The Team actively participated to societal events such as the annual AFM-Téléthon and ruffle fund-raising, during the Family Days where scientists and clinicians meet patients and families. It further contributed to dissemination of knowledge via teaching at the SU and Neuromuscular Research Center, and through the '1000 researchers in the school' program. Finally, the Team participated in the development of a smartphone application for the patients 'my realworld'.

Weaknesses and risks linked to the context

Co-operation with private partners could be reinforced.

Analysis of the team's trajectory

The team faces some challenges ahead. Notably, no integration of new members is explicitly planned in the new period. However, the Team combines a nice set of competencies that allows the Team leader, the project leaders, research assistants and clinicians to be internationally recognised for translation of their findings.
In the upcoming period, the Team can rely on the support of collaboration with one European grant (ERA-PerMed 2022–2025, 260kE) and support from 4 grants (ANR and AFM).
The future collaborations of the Team within the CRM and at the international level are well defined. In the future, the combination of cutting-edge approaches deployed by the Team can be expected to lead to impactful outputs.

RECOMMENDATIONS TO THE TEAM

The team needs to maintain its leader position in France on MG and its international recognition.
The team should strive to increase its standards of publication.
The team is well supported by Sorbonne University and the Association Institute of Myology but should develop collaborative research with private partners and with ERN-NMD.

Team 8: Muscle inflammation – Targetes and Innovative Therapeutics

Name of the supervisor: Olivier BENVENISTE & Yves ALLENBACH

THEMES OF THE TEAM

The Team is very translational and uses a bench to bedside (and back to bench) approach. They use deep phenotyping to gain knowledge into the pathophysiological mechanisms involved in inflammatory myopathies and develop innovative therapies.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

In agreement with the previous report, the team has attempted to obtain European grants, although not successful. The Team also increased its staff, allowing for more credible adequation to the Team's research ambitions.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	3
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	0
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	4
Sous-total personnels permanents en activité	**7**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	1
Post-doctorants	3
Doctorants	3
Sous-total personnels non permanents en activité	**7**
Total personnels	**14**

EVALUATION

Overall assessment of the team

Scientific production: Team 8 has an outstanding track record of publications (128 total with 51 as PDC). It produces a high number of outstanding research publications of high impact such as Lancet Rheumatol, Brain, JAMA Neurol, Nature Rev Rhumatol….

The team has excellent attractiveness, with numerous grants (2 ANR) and most being secured by foundations, and excellent international visibility (invitations to meetings, international collaborations, …)
The valorisation is outstanding, with exceptional translational outlook of the team, with several clinical trials being run by the group leaders. The team keeps excellent relationships with the industry through patents, research funding and partnerships.

Strengths and possibilities linked to the context

Team 8 has an excellent scientific reputation. Beyond an excellent track record of publication, tangible marks of scientific recognition lay in the numerous invitations to international meetings, including the Global Conference on Myositis, European League Against Rheumatism Congress, American College of Rheumatology Congress, World Muscle Society Congress, Autoimmunity Congress, and Myology Congress. For example, the team leaders are regularly invited to give lectures (41 for one of the Team leaders in the evaluation period).

Reinforcing this reputation, lab members also take an active part in dissemination of results to scientific audiences (87 oral/written presentations). Additionally, team leaders are reviewers for high impact journals (e.g. NEJM, Annals of Rheumatic Diseases, Brain, Nature Review). PIs also regularly organise national meetings. Finally, Team leaders are also members of scientific advisory boards for (National and International) grant selection as well as pharma companies. Team 8 is solid, being supported by two permanent Research Assistants, one of which having had his/her position secured during the evaluation period. Team 8 was recently joined by three new members, including one postdoc and one PhD student to develop projects through the next term.
Since 2017 Team 8 has hosted eight post-docs. It is also engaged in doctoral student supervision, with five completed theses during the mandate, two ongoing. The students under team leaders' supervision participated to reviews and conferences.
Finally, the team is excellent at securing national grants: €4.48 million were leveraged through various instances such as two ANR as PI, and ARC (315kE). To this adds up several grants obtained from foundations (AIM/AFM, 1498kE).
The publication track record is outstanding. It includes 128 total with 51 as PDC incl. Four reviews including the team leaders as co-authors during the last mandate, several of which in high-impact factor journals, as for example in Lancet Rheumatol in 2021. We note a good involvement of the team's staff in those publications. Importantly, the team has a strong translational outlook, leading to industrial outputs that are not easily assessed using regular academic metrics, but have a strong impact. These include conducting several clinical trials.
The team interacts with the industry: they apply and obtain competitive international private grants from the pharmaceutical industry (0.36 million euros: Shire®, Neovacs®, 2xSanofi®) and conducted eleven clinical trials. Thus, the contribution of the Team to the economic sector is excellent.
The team and its members in general have a strong track record of dissemination: press releases (INSERM, SU, AIM press offices) and targeted websites, radios or mainstream journals such as The Scientist and The Conversation – Regular participation to societal events like 'Fête de la science' (French science day), '1000 chercheurs dans les écoles', 'DECLICS2019', « Fête de la Science » – conferences or research training for undergraduate students and university open days to promote science research, higher education and community awareness – link researchers and families of patients including the 'annual AFM family day', creation of the association of myositis patients (Groupe d'Intérêt des Myopathies Inflammatoires GIMI) with the help of AFM. Team leaders participate to national and American meetings for patients (Journées des Familles Téléthon, The Myositis Association (TMA) yearly meeting)- Regular participation to French AFM-Telethon. The team & its medical department has a website for patients and doctors.

Weaknesses and risks linked to the context

Considering the size and productiveness of the team, securing additional permanent positions, including technical staff appears essential. The team does not appear to host foreign postdocs, which could enrich out of the box thinking in the team.
The committee raised a concern about the addition in the team of a new PI working on congenital myopathies, whose contribution is not very well articulated with the laboratory's main research interests.

Analysis of the team's trajectory

In the previous evaluation campaign, the team had set ambitious goals related to myositis research. They aimed to redefine myositis classification, understand molecular pathways in the disease, and propose targeted treatments. They successfully conducted four clinical trials based on a translational approach using clinical databases and biobank samples, allowing various analyses. The Team was strongly involved in initiating and conducting clinical trials, some with success and others less promising. The Team also faced technical issues hampering wetlab experiment progression, in particular muscle cell culture. They focused on improving muscle cell culture, fostering international collaborations, and implementing new RNA-Seq and single-cell analysis methods. These approaches allowed them to better understand muscle fibre necrosis and muscle immune responses, leading to the discovery of a new muscle cell subpopulation called resident memory T cells. Overall, the team made progress in understanding myositis and conducted clinical trials, but they faced setbacks and proved resilient and adaptable.
In the next five-year period, the team will focus on reaching three major objectives:
(i) Autoimmunity: Despite a growing number of clinical trials and opportunities for targeted treatments, remaining challenges include a shortage of eligible patients for randomised controlled trials. The team plans to use innovative approaches to palliate for this shortage.
(ii) Immune-Mediated Myotoxicities: The team choses a focus on Immune Checkpoint Inhibitors-associated myotoxicities. Through collaborations, the team plans to address challenges of gene therapy for muscle diseases in that context.
(iii) Muscle Homeostasis and Muscle Immunology: The team's research has demonstrated how the immune system can negatively impact muscle health. The Team will notably investigate the role of resident memory T cells in myositis and muscle regeneration, ageing, etc.
In sum, the team's research spans various aspects of muscle immunology, from understanding autoimmunity in myositis to addressing immune-mediated myotoxicities and exploring muscle homeostasis. To reach these

objectives, the Team has set a very realistic recruitment plan and acknowledges the requirement for inclusion of a higher number of permanent researchers in order to reinforce the fundamental aspects of their research. One of the most worldwide important experts in cardiotoxicities and his staff joined the team very recently and the Team will be joined by a specialist of congenital myopathies in 2024, bringing her expertise as a researcher but also as a clinician to reinforce the strategic vision for deciphering new biomarkers. They both aim to implement a multidisciplinary approach which appears well suited for their current environment with all resources available on campus.

RECOMMENDATIONS TO THE TEAM

The committee recommends strengthening the less translational aspects of the lab, notably by recruiting academic research scientists.
The committee recommends that the new group working on congenital core myopathies should be better connected with the rest of the team exclusively working on inflammatory myopathies.
The committee recommends increasing the number of applications for EU/international grants in particular, according to their outstanding track record and visibility.

Team 9: Signal pathways and striated muscles

Name of the supervisor: Antoine MUCHIR

THEMES OF THE TEAM

The team works on the cardiomyocyte nuclear envelope. The objectives are to understand the role of the proteins of the nuclear envelope and their link with the cytoskeleton and chromatin organisation, in health and disease conditions.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Following the previous recommendations, the team hired two additional permanent positions (IE and IR) in an effort to permit technical continuity. Publications were maintained in good to high impact journals. The research topics were re-centered around the molecular mechanisms connecting the cardiac nuclear envelope to the cytoskeleton, and the development of therapeutic approaches to treat CardioLaminopathies. Co-operation with industrial partners was extended during the last period. Outreach to the public was improved via press releases, letters on INSERM/University websites, and participation in the yearly Téléthon and '1000 researchers in school'.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	0
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	2
Personnels d'appui à la recherche	2
Sous-total personnels permanents en activité	**5**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	0
Post-doctorants	2
Doctorants	2
Sous-total personnels non permanents en activité	**4**
Total personnels	**9**

EVALUATION

Overall assessment of the team

The team is very well recognised for its work on the nuclear envelope and its associated cardiac diseases, in particular cardioLaminopathies. The team's permanent members have a very good complementarity of expertise leading to excellent scientific output, which includes the PhD students and postdoctoral fellows.

Scientific production is excellent, with 42 publications in total (14 as PI, in journals such as Nat Commun, Mol Cell, Cell Rep,..)

The attractiveness is excellent with diverse sources of funding (1/4 ANR contract as I), coming from national or international resources, many speaker invitations and active contribution to meeting organisation and presentation.

The valorisation is excellent with two patents and collaborations with industry.

Strengths and possibilities linked to the context

Team 9 has an excellent national and international visibility. The team leader started in the team of Team 1 and became independent in 2019. Team members have complementary scientific and technical expertise to decipher the pathomechanisms of envelopathies and test therapeutic options. The team has access to the largest patient tissue bank (MyoBank) and has several mouse and human cellular models (including iPSC) of envelopathies.
The team published more than 42 publications between 2017 and 2022, including fourteen original publications and 4 reviews as last author for the team leader. Ten publications are co-authored by at least one member of another CRM team. Team members are well integrated in the publications. The publications are in very good to high-impact journals, with the following highlights: 1) Mapping of ten different mononuclear cell types in adult mouse skeletal muscle (Mol Cell 2019). 2) Phosphorylated cofilin-1 binds to and prevents nuclear translocation of the MRTF-A/SRF complex, leading to reduced microtubule acetylation, delocalisation of connexin 43 and dilated cardiomyopathy in *Lmna* mutant mice (Hum Mol Genet 2019, Nat Commun 2022). 3) Nicotinamide riboside supplementation normalised NAD+ level and delayed cardiac dilation and dysfunction in *Lmna* H222P mice (Hum Mol Genet 2018). 4) *Lmna* mutant stem cells exhibit abnormal cardiac differentiation due to abnormal regulation of the chromatin architecture. The GSK-LSD1 dihydrochloride, inhibitor of lysine-specific demethylase one, prevents the development of cardiomyopathy in *Lmna* H222P mice (J. Clin Invest 2021 as collaborator). This led to an international Patent Application.

The budget was 1,405 k€ in 2017–2022. The team received four ANR (1 as PI, 3 as co-PI, total 909 k€), one emergence (PI, 67 k€), one région Occitanie (PI, 46 k€), AFM-Téléthon (PI, 270 k€), LeFoulon Delalande (PI, 70 k€), Fondation de l'Avenir (PI, 30 k€). Furthermore, the team leader and Allomke obtained a binational NIH grant to develop proprietary compounds for CardioLaminopathy.
The team leader has been invited to several national and international scientific meetings, and team researchers, postdocs and PhD candidates participated in 26 meetings. The team is involved in several national and international scientific or patient association networks. A team member has created a new national network on motor units (Filnemus-RCP).
The team leader was promoted to DR INSERM in 2022, a new CRCN INSERM was stabilised in 2021, and a new IE (SU) was recruited. During the last period, four students completed their PhD. Currently, two postdoctoral fellows and two PhD students are members of the team.
The team is well involved in transferring their knowledge to the public, incl. communication with letters to the universities and INSERM, dissemination through active participations in the '1000 researchers in school' action and Téléthon.

Weaknesses and risks linked to the context

A potential weakness is the association of very challenging projects for a young team.
Another one is the absence of European grants, which would be required to increase the visibility of the team.
Finally, the team should promote female scientists to balance the male project leaders in the future.

Analysis of the team's trajectory

The team's name will be 'Signalling pathways in CardioLaminopathies – SPATIAL' and the team is composed of 6 FTE (2 Inserm – 3 AIM – 1 SU).

In the next five years, the team strategy will focus on the cardiac tissue in lamimopathies, explaining the new name of CardioLaminopathies. The main objective of the team is to decipher the molecular and cellular mechanisms caused by defects in nuclear envelope leading to cardiomyopathy. The team will welcome a new PhD researcher, who was in another CRM team previously, expert of nuclear envelope and cytoskeleton of striated muscle. The team also plans to recruit additional permanent researchers, for instance, from the present postdoc through the INSERM tenured researcher competition. For the next period, the new Team will be composed of four groups working on 1) Cellular consequences of mutated nuclear envelope, 2) Cardiac metabolism alterations in CardioLaminopathy, 3) Tissue organisation of diseased heart and 4) Innovative therapies for CardioLaminopathy.

The association of these four subjects sounds very coherent and will bring the team to an even higher level of visibility with a strong scientific impact. With the use of state-of-the-art techniques such as the CRISPR/Cas9 genetic tools, iPSC-derived 3D muscle or heart organoids or micro-muscular tissues, out of others, the team will advance knowledge on the interaction and mechanical force between the nuclear envelope, lamin-associated domains, and cytoskeleton, signalling pathways, including altered metabolism involved in CardioLaminopathies and identification of potential novel targets for therapy.

The team will be instrumental within the CRM to accelerate research, diagnosis and therapeutic approaches, e.g. utilisation of gene editing tools to correct *LMNA* mutant cardiomyocytes (via the ANR grant Correct-LMNA), OMICs for cellular cartography of diseased human and mouse striated muscles resulting in a heart cell Atlas.

RECOMMENDATIONS TO THE TEAM

It is recommended to consider gender parity in the leading part of this team at least in the future, by promoting the female postdocs to permanent researcher positions.
It is recommended to explain how the team will handle the four groups in terms of resources (one PhD/post-doc per group?) and authorship (each group leader will be last author?).
The project #3 sounds very ambitious, and it would be useful to detail who/which team he plans to collaborate with.

Team 10: Neuromuscular Connectivity in health and diseases

Name of the supervisor: Laure STROCHLIC & Bertrand FONTAINE

THEMES OF THE TEAM

The goal of the team is to understand how the neuromuscular junction is established and maintained throughout life and how disruption of the communication between the brain and skeletal muscle leads to neuromuscular disorders, such as myasthenia and amyotrophic lateral sclerosis (ALS).

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous report recommended obtaining more competitive international grants. This issue has not been resolved, as the team is still dependent on French funding agencies. It was also recommended that the number of post-docs and PhD students should be increased. Two post-doctoral fellows and two PhD students were added to the team. Finally, it was recommended that the channelopathies project should not form part of the future scientific strategy, as it was not sufficiently research-oriented. Instead, during the last term, the team completed its work on channelopathies and a therapeutic trial on the effect of Mexiletine (a sodium channel blocker) on non-dystrophic myotonia was published.

WORKFORCE OF THE TEAM: in physical persons at 31/12/2022

Catégories de personnel	Effectifs
Professeurs et assimilés	2
Maîtres de conférences et assimilés	0
Directeurs de recherche et assimilés	1
Chargés de recherche et assimilés	0
Personnels d'appui à la recherche	3
Sous-total personnels permanents en activité	**6**
Enseignants-chercheurs et chercheurs non permanents et assimilés	0
Personnels d'appui non permanents	2
Post-doctorants	2
Doctorants	0
Sous-total personnels non permanents en activité	**4**
Total personnels	**10**

EVALUATION

Overall assessment of the team

The team has made important contributions in understanding diverse neuromuscular disorders, including amyotrophic lateral sclerosis, congenital myasthenic syndromes, and channelopathies. The team has complementarity expertise and the scientific production, especially on the function of Wnt signalling in neuromuscular connectivity, is very good (Curr Opinion in Physiol, Sci Signal).

The attractiveness and valorisation (2 patents) of the team are very good.
The sources of funding are very good and diverse, including national grants (2 ANR) and grants from patient associations (40% funding from AFM/AIM), but international contracts are missing.

Strengths and possibilities linked to the context

Since 2017, the team budget includes grants from 2ANR (as PI, total 546kE), SATT Lutech (380kE) and grants from patient associations (AFM-telethon, 500kE; , ARSLA, 63kE; , Fondation de l'Avenir, 35kE), for a total of around 2M

euros, including 40% funding from AIM. During the last period, five PhD students completed their thesis and three postdoctoral fellows (AFM-Telethon and ANR) were part of the team.

During the last mandate, the team has produced more than 40 publications (members are in leading position in Curr Opinion in Physiol, Sci Signal, Neurol Genet) and 4 reviews, and all the Master, PhD students, and research engineers are associated to the team publications as first, last or co-authors.
Members of the team have been invited to organise international conferences (B. Fontaine, Musclechannelopathies, ICNMD, Myology) or regularly invited for seminars and conferences in internationally recognised Institutes (I–Stem, Neuromyogene and Pasteur Institute for example) or during European/International congress (including EMBO, FENS and Neuromuscular meeting). B. Fontaine has been invited professor at the University of Columbus and Nationwide Hospital (Ohio, USA) in 2021.
The team obtained two patents and one licensed to AMO-Pharma.

Weaknesses and risks linked to the context

Weaknesses include the lack of international grants and weak participation in teaching.

Analysis of the team's trajectory

TEAM 10 will be dispersed

RECOMMENDATIONS TO THE TEAM

TEAM 10 will be dispersed

CONDUCT OF THE INTERVIEWS

Dates

Start: 22 novembre 2023 à 14 h

End : 24 novembre 2023 à 17 h

Interview conducted : on-site

INTERVIEW SCHEDULE

Day 1 — November 22, 2023 — Auditorium de l'Institut de Myologie, Bâtiment Babinski, Hôpital Pitié-Salpêtrière

14h-2:30 p.m. Presentation of committee members to team leaders over a cup of coffee

2:30 p.m.-2:45 p.m. Presentation of the committee to the audience

2:45 p.m.-3:45 p.m. Highlights of the Unit (20 mins) and trajectory (10 mins) by the Director
(30 mins of presentation, 30 mins of questions)

3:45 p.m.-4:15 p.m. Team 8: Inflammatory myopathies & innovative therapies (Benveniste)
15 mins of presentation, 15 mins of questions

4:15 p.m.-4:45 p.m. Team 7: Myasthenia Gravis: etiology, pathophysiological & therapeutic approaches (Le Panse)
15 mins of presentation, 15 mins of questions

4:45 p.m.-6:30 p.m. **Closed-door meeting of the committee**

Day 2 — November 23, 2023 — Salle Bordeaux, 5e étage du bâtiment 105 de la Faculté de Médecine SU

9h-9:30 a.m. Team 2: Muscle cell organisation and therapy of dominant centronuclear myopathy (Bitoun)
15 mins of presentation, 15 mins of questions

9:30 a.m.-10 h Team 1: Myomatrix & myonucleus related diseases: genetics and physiopathology (Bonne)
15 mins of presentation, 15 mins of questions

10h-10:30 a.m. Team 9: Signal pathways and striated muscles (Muchir)
15 mins of presentation, 15 mins of questions

10:30 a.m.-11 h Team 5: Gene therapy for DMD and pathophysiology of skeletal muscle group (Pietri-Rouxel)
15 mins of presentation, 15 mins of questions

11h-12:30 p.m. **Closed-door meeting of the committee**

12:30 p.m.-1:30 p.m. **Lunch**

1:30 p.m.-14 h Team 3: Cellular and molecular orchestration in muscle regeneration, during ageing and in pathologies (Trollet)
15 mins of presentation, 15 mins of questions

14h-2:30 p.m. Team 4: Repeat expansions & myotonic dystrophy (Furling & Gourdon)
15 mins of presentation, 15 mins of questions

2:30 p.m.-15 h Team 6: Biotherapies for motor neuron disorders (Smeriglio)
15 mins of presentation, 15 mins of questions

15h-3:20 p.m. Team 10: Neuromuscular connectivity in health and disease (Strochlic & Fontaine)
10 mins of presentation, 10 mins of questions

3:20 p.m.-6:30 p.m. **Closed-door meeting of the committee**

Day 3 — November 24, 2023 — Salle Bordeaux, 5e étage du bâtiment 105 de la Faculté de Médecine SU

9h-9:40 a.m. Meeting with technicians and administrative staff

9:40 a.m.-10:20 a.m. Meeting with PhDs and post-docs

10:20 a.m.-11 h Meeting with researchers not team leaders

11h-11:30 a.m. Meeting with the representatives of the local institutions

11:30 a.m.-12 h Meeting with the future team leaders

12h-12:30 p.m. Closed-door meeting of the committee

12:30 p.m.-13 h Meeting with the Director

13h-14h Lunch

14h-17h Closed-door meeting of the committee (report preparation)

17h End of the visit

PARTICULAR POINT TO BE MENTIONED

No particular point to be mentioned

GENERAL OBSERVATIONS OF THE SUPERVISORS

Marie-Aude Vitrani
Vice-Présidente Vie institutionnelle et démarche participative
Sorbonne Université

à

Monsieur Eric Saint-Aman
Directeur du Département d'évaluation de la recherche
HCERES – Haut conseil de l'évaluation de la recherche et de l'enseignement supérieur
2 rue Albert Einstein
75013 Paris

Paris, le 29 février 2024

Objet : Rapport d'évaluation – ICRM - Centre de recherche en Myologie
Cher Collègue,

Sorbonne Université vous remercie ainsi que tous les membres du comité HCERES pour le travail d'expertise réalisé sur l'unité de recherche « CRM ».

Sorbonne Université n'a aucune observation de portée générale à formuler sur le rapport d'évaluation transmis.

Je vous prie d'agréer, Cher Collègue, l'expression de mes cordiales salutations

Marie-Aude Vitrani
Vice-Présidente Vie institutionnelle
et démarche participative

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2 rue Albert Einstein
75013 Paris, France
T.33 (0)1 55 55 60 10

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