Research evaluation

EVALUATION REPORT OF THE UNIT

MMG - Centre de Génétique Médicale de Marseille (Marseille Medical Genetics)

UNDER THE SUPERVISION OF THE FOLLOWING ESTABLISHMENTS AND ORGANISMS:

Aix-Marseille université - AMU, Institut national de la santé et de la recherche médicale - Inserm

EVALUATION CAMPAIGN 2022-2023

GROUP C

Rapport publié le 23/08/2023

High Council for evaluation of research and higher education

In the name of the expert committee[1] :

Mr. Lucas Jacques Waltzer, Chairman of the committee

For the Hcéres[2] :

Thierry Coulhon, President

Under the decree n° 2021-1536 of 29th November 2021:
[1] The evaluation reports "are signed by the chairperson of the expert committee". (Article 11, paragraph 2);
[2] The president of the Hcéres "countersigns the evaluation reports established by the expert committee and signed by their chairperson." (Article 8, paragraph 5).

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 Lucas Jacques Waltzer, Centre national de la recherche scientifique, CNRS, Clermont-Ferrand
Experts:	Ms Christine Bellanne-Chantelot, Sorbonne Universités (representative of CSS) Mr Frederic Checler, CNRS, Sophia-Antipolis Mr Cyril Goizet, université de Bordeaux (representative of CNU) Mr Christophe Le Clainche, CNRS, Gif-sur-Yvette Ms Laurence Pibouin Fragner, Inserm, Paris (representative of research supporting personnal) Mr Lucas Jacques Waltzer, CNRS, Clermont-Ferrand

HCÉRES REPRESENTATIVE

Ms Marie José Stasia

CHARACTERISATION OF THE UNIT

- Name: Marseille Medical Genetics
- Acronym: MMG
- Label and number: U1 251
- Number of teams: 8
- Composition of the executive team: Dr. Frédérique Magdinier

SCIENTIFIC PANELS OF THE UNIT

SVE Sciences du vivant et environnement

SVE3 Molécules du vivant, biologie intégrative (des gènes et génomes aux systèmes), biologie cellulaire et du développement pour la science animale

THEMES OF THE UNIT

The Marseille Medical Genetic Center (MMG) develops research focused on understanding the mechanisms leading to rare developmental diseases of the heart, the muscular system, the nervous system or the neuroendocrine tissues, as well as to pathologies associated with nuclear envelope proteins defects, including premature aging.

The unit is organised along four research departments: 'central nervous system and neuroendocrine disorders', 'nerve and muscles', 'development and patho-physiology of cardiovascular development', 'prenylation in ageing and cancer', each of them constituted by one to four teams. It also comprises five technological platforms (facility for *in vivo* experimental models; Stem cells culture; Genomics and bioinformatics; Imaging; Biological resources).

For the evaluation period, the unit was composed of ten teams:
- Team 1: Human Neurogenetics, directed by Laurent Villard.
- Team 2: Ageing, Prenylation & Cancer, directed by Nicolas Levy.
- Team 3: Translational Neuromyology, directed by Marc Bartoli.
- Team 4: Genetics & Development of Cardiac Defects, directed by Stéphane Zaffran.
- Team 5: Epigenetics, Chromatin and Disease Modeling, directed by Frédérique Magdinier.
- Team 6: Bioinformatics and Genetics, directed by Christophe Beroud.
- Team 7: Pathophysiology of Cardiac Development, directed by Michel Pucéat.
-Team 8: Differentiation and Proliferation of Neuroendocrine Tissues, directed by Thierry Brue.
-Team 9: Cardiovascular Calcification and Pathologies, directed by Anabela Bensimon-Brito (created in 2021, not evaluated).
- Team 10: Normal and Pathological Cardiopharyngeal Mesoderm Development, directed by Fabienne Lescroart (created in 2020, not evaluated).

HISTORIC AND GEOGRAPHICAL LOCATION OF THE UNIT

The MMG (UMR1251) is a mixed unit affiliated to Inserm and Aix-Marseilles Université (AMU). It was created in 2018 as a follow up to the Medical Genetics and Functional Genomics unit (GMGF, UMRS_910; 2008-2017). It is located on Marseille Medical School/Hospital La Timone Campus, within the School of Medical and Paramedical Sciences.

RESEARCH ENVIRONMENT OF THE UNIT

The MMG is part of the 'campus Hospitalier de La Timone', with which it has established strong links, in particular with the Department of Medical Genetics and Cell Biology.

The unit is one of the founding members of the Marseilles Maladies Rares University Institute 'MarMaRa' (headed by T. Brue) created in 2019 with the support of Aix-Marseille Idex (Amidex). All the MMG teams are affiliated to MarMaRa. The unit also belonged to the Federative Hospital University (FHU) program' Maladies Rares et Chroniques » (headed by N. Levy, 2015-2018), which brought together clinical and research teams on rare disease with patient organisations and industrial partners.
The unit is associated with several National or European reference centres for rare diseases (e.g. intellectual deficiencies of rare cause, pituitary disorders, neuroendocrine diseases…) and contributes to Inserm Human Developmental Cell Atlas program (HuDeCa).

Some teams take part in steering committees for Amidex or benefit from support of the PIA-funded Institut de Convergence Centuri.

One of the five MMG technological platform (Stem Cells) belongs to the network of AMU certified platform.

UNIT WORKFORCE: in physical persons at 31/12/2021

Permanent personnel in active employment	
Professors and associate professors	19
Lecturer and associate lecturer	14
Senior scientist (Directeur de recherche, DR) and associate	11
Scientist (Chargé de recherche, CR) and associate	9
Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées)	0
Research supporting personnel (PAR)	37
Subtotal permanent personnel in active employment	90
Non-permanent teacher-researchers, researchers and associates	5
Non-permanent research supporting personnel (PAR)	12
Post-docs	12
PhD Students	52
Subtotal non-permanent personnel	81
Total	171

DISTRIBUTION OF THE UNIT'S PERMANENTS BY EMPLOYER: NON-TUTORSHIP EMPLOYERS ARE GROUPED UNDER THE HEADING 'OTHERS'.

Employer	**EC**	**C**	**PAR**
Aix-Marseille Université	32	0	19
Inserm	0	16	7
CHU Marseille	1	0	11
CNRS	0	4	0
Total	33	20	37

UNIT BUDGET

Recurrent budget excluding wage bill allocated by parent institutions (total over 6 years)	2373.0
Own resources obtained from regional calls for projects (total over 6 years of sums obtained from AAP idex, i-site, CPER, territorial authorities, etc.)	155.0
Own resources obtained from national calls for projects (total over 6 years of sums obtained on AAP ONR, PIA, ANR, FRM, INCa, etc.)	13,704.0
Own resources obtained from international call for projects (total over 6 years of sums obtained)	4761.0
Own resources issued from the valorisation, transfer and industrial collaboration (total over 6 years of sums obtained through contracts, patents, service activities, services, etc.)	0.0
Total in euros (k €)	14,851.0

GLOBAL ASSESSMENT

The Marseille Medical Genetic Center (MMG) develops various lines of research focused on understanding the mechanisms underlying the development of rare human genetic diseases. It has a strong valence toward biomedical and clinical projects in association with the neighbouring Hospitals of La Timone and Conception. The themes of the eight teams encompass developmental diseases of the heart, the muscular system, the nervous system or the neuroendocrine tissues, as well as to pathologies associated with nuclear envelope proteins defects, including premature aging. To study these diseases, the teams use various cellular models (including pluripotent induced stem cells and primary cells) as well as a mammalian model and zebrafish, and a combination technique ranging from genetics to molecular biology and bioinformatics.

The overall functioning of the unit is excellent, with a broad but clearly well-shared scientific objectives and a strong bench-to-bed-side culture for of most of the team. The unit benefits from well-established platforms particularly for genomics, imaging and human induced pluripotent stem cells culture. However, some premises of the unit, such as the facility for in vivo experimental models, and space limitations or decrepit rooms are a matter of concern.
With 878 articles, the unit has been extremely productive and the overall level of publication ranges from very good to excellent, with many articles as lead authors in recognised specialty journals or more generalist journals (e.g. American Journal of Human Genetic, Bioinformatics, Cardiovascular Research, Development, eLife, Embo Molecular Medicine, European Journal of Endocrinology, Human Molecular Genetics, Journal of Clinical Investigations, Nature Communications, Nature Genetics, Nucleic Acids Research, Sciences Advances). The proportion of high-profile publication could be improved, but it should be noted that working on rare disease tends to funnel many publications toward specialised journals.
The attractiveness of the unit is excellent to outstanding as demonstrated by the arrival of 2 new ATIP/Avenir teams (including an ERC laureate) and the recruitment or arrival of 41 new staff personals. Of note, the emergence and/or recruitment of four new team leaders will strengthen the research potential of the unit in the domain of cadio-vascular research and is expected to rejuvenate its dynamic in the field of bioinformatics. The unit collected 18.6M€ through in competitive calls from 2016 to 2021. Thus external funding represented around 85% of the unit budget. These fundings included two major AFM-Telethon grants and 5.2M€ of international contracts. The MMG also obtained six important grants from the local PIA-funded project Amidex and it participated in the foundation of the Marseille Maladies Rares university institute in 2019, with a clearly positive impact for the unit.
The visibility of the unit is well attested by more than 250 invitations or selection for oral presentations in conferences and meetings, by the organisation of nineteen conferences and implication in various learned societies at the national and European levels. Visibility is particularly strong in the fields of neuroendocrine diseases, neurogenetics, progeria, cardiology and bioinformatics. The national and international reputation of the unit as a reference centre for different rare diseases (e.g. intellectual deficiencies of rare cause, pituitary disorders, neuroendocrine diseases) is very well established too. Accordingly, many unit members stand as experts for patient associations or health authorities and contributed to recommendations for the diagnosis and/or care of genetic diseases.
As a whole, the socio-economic interactions of the unit are excellent to outstanding. There are strong links with the industry as shown by several contracts for the development of new therapeutics or human cell lines. Beside its implication in clinically-oriented projects (association with 10 patient's database, creation or management of 11 cohorts and collection of human biological samples, contributions to 8 clinical trials), the unit filed twelve patents and six inventions and it created three start-up companies.

Finally, in line with its biomedical thematic, the unit is strongly associated with patient organisations (AFM-Telethon, Rett Syndrome…) and it is engaged in many communication and outreach activities toward the general public and young students.

DETAILED EVALUATION OF THE UNIT

A - CONSIDERATION OF THE RECOMMENDATIONS IN THE PREVIOUS REPORT

Overall, the different recommendations of the previous committee were adequately taken into consideration.

Scientific quality and outputs.
The previous committee advised to concentrate more on work that will lead to first/last author publications in high impact journals. With 43% of publications signed as first or last author as compared to 33% in the previous mandate and the majority of those published in reputable journals, this recommendation has been fulfilled in good part.

Academic reputation and appeal.
The main recommendation was to raise the unit international visibility and standing (greater attendance at international meetings, attracting skills from abroad, strengthening international collaborations and fundings). Overall, these recommendations were followed: unit members gave oral presentation to more than 200 meetings (mostly international), participated in international conference organisation and maintained productive international collaborations. Of note, all the eight teams obtained some international and/or European funding (5.2 million euros in total). The unit also recruited 41 new staff personals, including two new PI with ATIP funding (one recently obtained an ERC Starting grant) and 34 postdoctoral fellows among which 47% were international fellows.

Unit organisation and strategy.
It was suggested to delegate more management tasks and responsibilities to junior researchers and engineers as well as to give more assistance to the unit director. The implication of the different categories of personals in the unit life and organisation has been reinforced and a deputy director was nominated at the beginning of the contract. However, the unit did not benefit from further administrative support.

Training.
The committee recommended to increase the recruitment of international student. During this contract, 21% of the PhD students came from abroad.

B – EVALUATION AREAS

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

Assessment on the unit's resources

MMG benefits from excellent resources both in terms of human potential, scientific expertise, technological platforms and funding. Its activity profile is very well integrated in its local environment, in particular with the Hospital La Timone. However, the premises of the unit are a source of concern and may hamper its development as a flagship of research on rare diseases.

Assessment on the scientific objectives of the unit

The scientific policy of the unit is excellent. The unit has clear and coherent scientific objectives, which are very well shared between all the teams beside their apparent thematic diversity. By investigating the genetic, developmental and molecular bases of various rare diseases, the unit has developed strong and valuable links with clinical research. The recruitment of two new teams and the emergence of new PIs fit well with the unit strategy and should compensate for departure of other teams. Yet, the scientific policy of the unit would benefit from a higher pooling of resources and a stronger involvement of the SAB in team recruitment/organisation.

Assessment on the functioning of the unit

Although the unit has faced some profound changes in its direction and structuration in the course of the evaluated period due to the abrupt cancellation of the Giptis project by the APHM, these turmoils did not undermine the excellent functioning of the unit. The overall management of the unit is well structured and the unit complies with its institutional requirements in terms of health and safety, quality management or data protection. The scientific life of the unit is well organised and the different categories of personal appear satisfied.

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

Strengths and possibilities linked to the context

The MMG develops interesting lines of research related to rare human genetic diseases, with a strong valence toward biomedical and clinical projects in association with the neighbouring Hospital of La Timone. It presents an excellent combination of personal and financial resources as well as a well-structured managerial organisation and strong platforms to perform its missions efficiently.
The human resources of the unit have strongly increased during the contract, notably with the arrival of several researchers/teacher-researchers (13) and support staffs (8) from the neighbouring institutes (CRN2M, CRCM, IBDM, I2M...), but also with recruitments of new researchers (3 including 1 in 2022) and support staff (5). These arrivals largely compensate the departures of nine researchers and thirteen support staffs from the unit, although more departures are expected for the next contract and some uncertainties remain concerning the fate of part of Team 2 (ex N. Levy).
The unit exhibits an excellent level of funding thanks to its capacity to obtain external contracts (about 80% of its budget for the period under consideration). The support by its two supervising bodies (Inserm and AMU) has been relatively stable over the period (about 390k€/year).
The MMG is well integrated in its environment and has been pro-active in exploiting the opportunities provided by the PIA: the unit spearheaded the creation of the University Institute MarMaRa (Marseilles Maladies Rares, headed by T. Brue) and all the teams are associated to this Amidex initiative. Some teams also benefit from the PIA-funded Institut de Convergence Centuri. At the national level, the unit was a founding member of the federative Hospital University (FHU) program MaRChe (Maladies Rares et Chroniques, headed by N. Levy, 2015-2018) and the unit participates in the Inserm projects Agemed, Gold and Hudeca.
The unit has established four very good technological platforms which provide support for imaging, breeding and phenotyping of *in vivo* experimental models, NGS sequencing and bioinformatic analyses, cell reprogramming and stem cell culture. The unit makes regular investment in equipment to maintain or increase its operational capacity (1.9M€ since 2016, around 12% of its budget). Notably, funding from the Leducq foundation allowed it to buy cutting-hedge microscopy equipment (slide scanner AxioScan1, AxioObserver 7, confocal microscope LSM800
Another strong asset of the unit is its access to human biological samples and large cohort of patients thank to its links with the biological resource centre of the Hospital La Timone and its role in national or European reference centres for rare diseases.

Weaknesses and risks linked to the context

Around one third of the institutional resources is distributed between teams and there is no levy on team contracts. This somehow limits the operational capacity of the unit management team to provide support for specific actions such as investment in new equipment, hiring of support staff, or room refurbishment.
Along that line, the premises of the unit do not seem to be up to the expected standards. Indeed, refurbishments of the premises have been stalled for several years with the development of the Giptis project, which has recently been cancelled. As a result, the unit had to spend 88k€ on its own funds to maintain some basic infrastructures. Urgent investments are needed to renovate some labs and offices as well as to allocate more spaces to the unit. The situation of the facility for *in vivo* models is also an important matter of concern as delays in the establishment of the new facility resulted in extra-costs for breeding and was detrimental for several scientific projects.

A large part of the financial resources (30%) comes from a major grant from a single entity (AFM). Although this grant was renewed for 2021-2025, this important dependence of the unit to the AFM represents a risk.

The proportion of technical agent to researchers is slightly below the national average (0.55 <0.65), and the technical platforms are understaffed.

The abrupt cancellation of the Giptis project and the departure of N. Levy's team weakened the unit prospective.

2/ The unit has set itself scientific objectives, including the forward-looking aspect of its policy.

Strengths and possibilities linked to the context

The MMG has a well-established identity and the overarching scientific objectives are shared between the teams. The unit has excellent expertise and very good international visibility in the fields of developmental diseases of the heart, the muscular system, the nervous system and neuroendocrine tissues, as well as in aging and cancer.
Research at the MMG takes advantage of a valuable combination of genetics, epigenetics, bioinformatics, system biology and developmental biology approaches and makes use of cellular (including hiPSC) or higher organisms (small mammals and zebrafish) to identify new genes implicated in human pathologies (with important implications in terms of diagnostics), study the underlying cellular mechanisms, develop preclinical models and design new therapeutic strategies.
Importantly, there is a salient continuum between the research activities of the unit and care structures and a strong bed-to-bench two-way transfer culture. Accordingly, most teams are deeply involved in patient-oriented research projects in the context of genetic diseases and they benefit from high-level clinical expertise and excellent access to samples.
The scientific objectives of the unit are sound, original and fully in line with the policy of the supervising bodies. The research is particularly relevant in terms of human health and tackles important societal challenges. This is exemplified by the unit's leading role as a reference centre for different rare diseases, involvement in eight clinical trials, development of new diagnosis tools or strong interactions with patient associations. The unit also has numerous links with the socio-economic sector (several industrial contracts, 12 patents, creation of 3 start-up…) and it is very much involved in teaching, notably in the field of medical genetics with the creation of the professional master 'genetic counselling and predictive medicine' or teaching in MarMaRa PhD program.
The unit has been able to mobilise important resources to acquire new equipment to conduct its strategy. Besides, it recruited new team leaders to reinforce research on cardiac/cardiovascular development and disease, which was already a strong asset of the unit, and to implement innovative system biology approaches. The unit also recently set up a scientific advisory board, which will help define its future scientific orientations.

Weaknesses and risks linked to the context

The common theme 'rare disease' is vast and covers a variety of research lines across the unit, which may hamper the interactions between teams and eventually marginalise some of them.
The role of the four departments is not clear and their definition could be improved. Along the same line, the contour of some teams is not very well defined; several teams conducted two or more axes of research headed by different PI's with sometimes limited interactions between them or on apparently unrelated topics.
While the unit has been very successful in attracting new PIs, the procedures to create new team or to structure team/unit (re)organisation, as well as the unit strategic orientations do not seem clearly established. As mentioned previously, the limited resources available to the direction of the unit also limits its capacity to further develop its scientific policy (start-up packages, incentive actions…).

3/ The functioning of the unit complies with the regulations on human resources management, safety, the environment and the protection of scientific assets.

Strengths and possibilities linked to the context

The human resource management of the unit is fully appropriate. Adequate measures are taken to promote non-discrimination and to ensure the security of all the staffs. The unit applies the rules relative to HR Excellence in Research, a certification given to AMU and Inserm by the European Commission. Newcomers are greeted with an annual welcome meeting and provided with an electronic booklet containing the necessary information about internal regulations, safety rules… Health and safety issues are very well cared for.
The different rules applying for the use of live complex models, GMO, patient samples or databases are very well taken into consideration and implemented.
The unit is strongly committed to promote scientific integrity and quality as well as the FAIR principles. Notably, it participates in the Réseau Inserm Quality, it has set up a quality management system and implemented the

usage of Inserm electronic notebook (Labguru). Until recently, the IT support was handled internally by a research engineer and the unit has set up a centralised data storage and sharing system.

The gender balance is excellent at the unit level (59% women - 41% men). Although this balance is not maintained when we consider the heads of the teams (1 woman vs 7 men), this should drastically change in the next period (6 women vs 3 men).

The unit atmosphere also seems excellent, with regular social events in addition to a very good level of scientific animation (weekly internal and external unit seminars in addition to team meetings). The different categories of personals did not voice major or very specific concerns and they seem very much satisfied with the management of the unit, teams and platforms.

Classical measures to promote sustainable development are in place.
An activity continuity plan has been set up and the Covid crisis was well managed.

Weaknesses and risks linked to the context

The unit does not seem to have clearly established procedures to take psychosocial risks into account.
The implication of the unit in reducing its carbon footprint is still limited, but further actions would probably require institutional support.

The unit and its various staffs mentioned difficulties in securing access to a functional *in vivo* experimental model facility, frequent risks of power shortages in the building and limited/inadequate office/lab space, generally poor building conditions, as well as IT problems (e.g. unexpected reallocations of IP adresses). There seems to be important discrepancies between the needs of the unit and the support of the host institution(s) concerning basic infrastructure and administrative issues.

EVALUATION AREA 2: ATTRACTIVENESS

Assessment on the attractiveness of the unit

The attractiveness of the unit is excellent to outstanding, as shown by the arrival of two new ATIP/Avenir teams, the recruitment or arrival of 41 new staff personals, 34 postdocs and 67 PhDs. Moreover 82% of its budget comes from external funding with a large amount of international grants. The unit also developed valuable technological platforms in particular for induced pluripotent stem cells cultures. The international reputation of the unit is well attested by the participation in journal editorial boards and international research consortiums as well as by invitations to international conferences.

1/ The unit has an attractive scientific reputation and contributes to the construction of the European research area.

Strengths and possibilities linked to the context

The scientific reputations of the unit is well established, as demonstrated by the numerous invitations or selection for oral presentations in conferences and meetings (>250), including in some prestigious international conferences (Gordon, Embo, Keystone, Society for Neurosciences, Endocrine Society, Enea, European Society of Cardiology…). They have also contributed to the organisation of nineteen conferences, mostly national but also for the FSH international society, the Human Genome Variation Society, the European Society of Cardiology, or the annual congress of Endocrinology. In every team, at least one researcher stands in the editorial board of a peer-reviewed journal (18 journals in total, such as: Cells & Development, Frontiers in Endocrinology, IJMS, J. Cardiovascular Development & Disease, J. Neuroendocrinology, Human Mutation, Peer J…).

The implication of the unit in various learned societies (>30) is very strong, in particular in the neuroendocrine, neurogenetic, cardiology and bioinformatics fields. Besides, twelve unit's members participipate in different institutional committees (Inserm CSS 1, Inserm GRAM, CNU44, Medical study ECN; HAS…) or charities scientific/expertise boards (Association Française du syndrome de Rett, Fondation ARC, Fondation de France, Fondation Maladies Rares, Ligue contre le Cancer…).

Weaknesses and risks linked to the context

While some teams have a very strong international reputation, the thematic diversity of the unit probably hinders its global visibility.
Invitations to international congresses are essentially limited to a small number of members with excellent visibility.

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

Strengths and possibilities linked to the context

The attractiveness of the unit during this period is clearly remarkable.
Notably, the unit recruited two new team leaders who both obtained an Inserm research position as well as competitive funding from the ATIP-Avenir program, and one of them will be funded by an ERC starting grant. Another two researchers from neighbouring institutes joined the unit at the beginning of the mandate with the perspective to have their own team for the next contract. Beside these two emerging team leaders, several staffs (8 researchers, 5 MCU/PU-Ph, 8 support staffs) from other institutes (essentially in Marseilles) joined the unit to participate in the creation of Team 8 (headed by T. Brue) in 2017 or to reinforce other teams.
In addition, the MMG benefited from the recruitment of one Inserm junior researcher, two MCU-PH, and three technical staffs. Moreover, a very high number of support staff (17) obtained a promotion during the contract. These recruitments and promotions were probably boosted by the unit 'Bococo' mentoring program set up in 2013, which is an excellent initiative.
At the more junior level, the unit was also very attractive: it hosted 67 PhD students (29 on going) and 34 postdocs.
The unit has taken good measures to promote open science, which is also financially encouraged by AMU, and 65% of the unit publications are freely available.

Weaknesses and risks linked to the context

Given the number of HDR present in the institute (around 50), the number of PhD students could be increased. The duration of the PhD has reached 48 months recently, probably due to the sanitary crisis, and not all the PhD obtained a first author research publication. The recommendation of the doctoral school to have a (single) thesis committee by the end of the second year of training does not seem optimal and PhD students did not always feel that they had the possibility to voice their problems to independent peers. Also, an online course to sensitise PhD students to integrity and ethics may not be the most efficient measure.

3/ The unit is attractive because of the recognition gained through its success in competitive calls for projects.

Strengths and possibilities linked to the context

The capacity of the unit to obtain funding is excellent. From 2016 to 2021, the unit collected 18.6M€ through in competitive calls. Thus external funding represented around 85% of the unit budget. This remarkable result is in good part attributable to two major AFM-Telethon grants (30% of the budget). The unit received consequent international funding (5.2M€) notably through two Leducq Fondation grants and nine European contracts (2 FP7, 2 H2020, 1 ERA-NET, 1 EJPRD, 1 IMI, 1 Europe R-RARE, 1 MSCA). At the national/regional level, MMG teams participated in 24 ANR (12 as coordinator, incl. 2 ANR-JCJC), two INCa, five program grants from Inserm and a handful from various other sources. The level of funding with charities (mainly from the AFM-Telethon) is also impressive with 32 grants as coordinators and several as partners.
The MMG also makes excellent use of local/regional opportunities. It obtained six important grants from AMU Amidex and one from APHM and it participated in the foundation of the MarMaRa university institute in 2019.
The important resources of the unit allowed it to invest in equipment, but also to hire postdoc, students and technical staffs, with a mean of 34 persons per year employed on short-term contracts.

Weaknesses and risks linked to the context

The dependency on AFM contracts is important.

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

Strengths and possibilities linked to the context

The MMG has a very good set of platforms with state-of-the-art apparatus. Its regular investment policy and the gain of specific grants from foundations or the region allowed it to maintain or upgrade several equipments notably for imaging, phenotyping and next generation sequencing. The four platforms are generally well organised, with dedicated committees to evaluate their needs, and support staff to run the instrumentation and/or provide on-site training for users. Three out of four platforms are open to external users and the Marseille Stem Cell facility was particularly successful in attracting external users (50% of its activity) notably from the industrial sector. MMG also has a collaboration with Zeiss for its imaging platform, which makes it attractive. As part of the quality management system implemented in the lab since 2018, customer satisfaction surveys are in place for each platform.

Weaknesses and risks linked to the context

The platforms are generally understaffed due to limited number of permanent agents in the unit and part of their functioning relies on researcher directors with already heavy burden.
The relocation of the facility for preclinical models has been delayed, which hindered several projects and caused increased costs for users. The support offered by the genomic/bioinformatics platform is also under important strain with the departure of one agent and the ongoing reorganisation of the unit.

EVALUATION AREA 3: SCIENTIFIC PRODUCTION

Assessment on the scientific production of the unit

The scientific production of the unit is very good to excellent and heterogenous between teams. With 878 articles, including 487 research publications, the unit has been extremely prolific thanks to the contribution of most unit members. The majority of the research articles was published in well-established specialty journals, notably in the human genetic field, reflecting the strong quality of the research performed in the unit. The proportion of open-access manuscripts is good (65%), but the proportion of higher profile publications and of co-publications between teams could be improved.

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

Strengths and possibilities linked to the context

The unit has been extremely productive. From 2016 to 2021, it published 878 articles, including 292 clinical publications and 487 research publications, as well as eleven book chapters in English, which is remarkable given the size of the unit (35 MCU/PU-PH, 1 MCF & 26 CR/DR hosted during the period). Of note, 43% of the research articles were signed as first or last author by members of the unit, a strong increase in comparison with the previous evaluation period. The majority of the research articles were published in well-established journals, notably in human genetic, neurology, endocrinology or molecular biology. This reflects the strong quality of the work performed in the unit. Although the production is quantitatively very heterogenous among the teams, notably due to their different in size, most of them produced some important results, which they published as lead authors in excellent specialty journals or more generalist journals (e.g. American Journal of Human Genetic, Bioinformatics, Cardiovascular Research, Development, eLife, Embo Molecular Medicine, European Journal of Endocrinology, Human Molecular Genetics, Journal of Clinical Investigations, Nature Communications, Nature Genetics, Nucleic Acids Research, Sciences Advances) (cf. team by team analysis).

Weaknesses and risks linked to the context

There is a notable level of disparity between teams in terms of visibility of the publications, which is partly explained by the specificities of the different thematic fields. Still, a number of publications do not reach very high standards and many of them seem funneled toward publishers with controversial editorial policies. While this is certainly a practical way to publish sound findings in a timely manner, this solution should be considered with caution.
The proportion of inter-team publications remains limited (<20%) and unbalanced between teams (e.g. team 2 contributed to 50% of all the co-publications and 33% of them involved only team 2 and one other team).

2/ Scientific production is proportionate to the research potential of the unit and shared out between its personnel.

Strengths and possibilities linked to the context

Overall, all the categories of personal are associated to the production of the unit. In general, PhD students and postdocs sign publications as first or co-author, and the positioning of staff scientists depends on their role in the project. Technical staff are also included as authors in publications.
All the teams have been productive, albeit with differences in volume and level of production that are partly explained by the specificities of the different thematics and the heterogenous size of the teams.

Weaknesses and risks linked to the context

No major weakness was identified.

3/ The scientific production of the unit complies with the principles of research integrity, ethics and open science.

Strengths and possibilities linked to the context

In the last three years, the MMG has implemented a quality management system to improve the organisation, traceability and reliability of scientific research results. It also follows classical measures to promote scientific integrity. The work is on the whole published in reliable peer-reviewed journals. Some efforts have been made to provide open access to the published manuscripts using deposition in HAL (65% of MMG publications).
Regulatory rules concerning human-based material usage or patient inclusions are followed. Procedures are submitted to ethical committee, infrastructures are accredited and experimenters follow specific trainings.

Weaknesses and risks linked to the context

The authorship policy is not formally defined at the unit level or through general guidelines in the 'réglement interieur' but essentially relies on the PI decision. It should be stressed though that the different categories of staff did not raise this as an issue.
The proportion of publication by some teams in journals with controversial editorial policy is a slight matter of concern.

EVALUATION AREA 4: CONTRIBUTION OF RESEARCH ACTIVITIES TO SOCIETY

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

The unit's interactions with the non-academic world are excellent to outstanding. The main strength of the unit is its interactions with the hospital for the diagnosis and treatment of rare diseases, which are at the core of its scientific strategy: it developed various genetic databases, cohorts and sample collections at the national and European levels, and it is involved in clinical trials. With twelve patents and three start-up companies, the economic valorisation of the unit is also very strong. Several teams have sustained contacts with patient associations and/or make exceptional contributions to outreach activities toward the general public.

1/ The unit stands out by the quality of its non-academic interactions.

Strengths and possibilities linked to the context

The interactions of the unit with the non-academic sectors are very strong. In particular, the MaSC platforms has numerous contracts with industries (LVMH, AtmosR, CECS, Neuron Experts). It developed new therapeutic solutions in connection with different pharma companies notably (for example: Novartis: MAP kinase inhibitors; Inventiva: Yap/Tead inhibitors; Pfizer: acromegaly modeling). Some teams obtained Cifre PhD grants together with the companies such as ProGeLife (created in 2014 by Team 2 members), and many PhD students were funded thanks to contract with patient associations. Non-academic contributions also helped recruit technical staffs on short-term contracts.
In addition, MMG has very strong interactions with several patient associations, in particular the AFM-Telethon, and the foundation Fondation Maladies Rares.

Weaknesses and risks linked to the context

No significant weakness was identified.

2/ The unit develops products for the socio-economic world.

Strengths and possibilities linked to the context

MMG is involved in research with direct impact on human health. The socio-economic impact of the unit is clearly excellent. MMG participates in patient's database, created or managed eleven cohorts and collection of human biological samples and contributed to eight clinical trials. It deposited twelve patents, six inventions and thirteen softwares. They also contribute to expertises by various health authorities or patient associations' scientific committees, and are involved in different centres of references for rare diseases networks. They contributed to national or international recommendations for care of rare diseases. Three start-up companies were created as spin-offs from research teams (Genomnis, Calysens, NeoFlow therapeutics). Creations of other start-ups are in discussion with the SATT Sud-Est and with BPI-France.

Weaknesses and risks linked to the context

The level of valorisation is heterogenous among the different (sub) teams.

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

Strengths and possibilities linked to the context

The interactions with the general public are excellent. The unit spearheaded the creation of the Recherch'thon association and most of the teams are strongly involved in outreach activities under the tutelage of AFM-Telethon or other patient associations. They regularly participate in action of diffusions toward the general public or the younger scholars (Pint of Science, Fête de la science, Semaine du Cerveau, Déclic…). Several MMG members were invited to present their results or to disseminate scientific ideas in TV or radio broadcasts and national or regional press articles. Unit members also produced didactical tools and are active on social networks.

Weaknesses and risks linked to the context

None identified.

C – RECOMMENDATIONS TO THE UNIT

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

The disease-oriented research of the MMG should remain at the centre of its activity profile. Maintaining and tightening the links with the Hospital will be essential to achieve its goals.

To facilitate bench to bed-side research in all the teams, it will be important to integrate clinicians in the new teams.
The definition and structuration of the department could be reconsidered. Along the same line, the identity of the teams could be improved, with a clearer focus on a common scientific goal for some of them.

The unit should aim at building a stronger communal budget to increase its operational capacity and its means for incentive actions.

It will be important to help the future director for management of the unit and participation in various local committees. As a large executive board may not be very efficient, the nomination of a deputy director with a complementary profile (e.g. links with the university/hospital) should be envisioned.

Stabilisation of facilities and a general refurbishment of the unit's premises are essential to maintain its activity and its attractiveness.
Marseille Stem Cell Core facility also requires permanent staffs for its management as the prospective unit director shouldn't be expected to directly run this platform.

It is recommended that an internal correspondent for psychosocial risks is nominated.

Recommendations regarding the Evaluation Area 2: Attractiveness

The unit has been remarkably attractive during the evaluated period but also lost some strong elements and at least two other team leaders are poised to change affiliation. The demise of the Giptis project should not stall the ambition of the unit to attract new leaders in the field of rare diseases. To enhance its visibility, the unit should make greater use of open calls for the recruitment of new teams. It should also take advantage of the recent restructuration of the unit to define its strategic requirements in terms of thematics, expertise and instrumentation. It is expected that the SAB will be closely associated with those actions.

The unit should strive to further increase its integration in European/international consortia related to rare diseases.
It will be important also to strengthen the bioinformatic support provided by the platform.

Recommendations regarding Evaluation Area 3: Scientific Production

Efforts should be pursued to publish research in well-esteemed journals and to increase the proportion of publication in leading journals. There is also room for improvement concerning the proportion of publications in open access.

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

The socio-economic interactions of the unit and its implication in outreach activities constitute a strong asset that must be maintained or expanded. The committee recommends that the unit continues to develop tight links with industrial partners and patient associations.

TEAM-BY-TEAM ASSESSMENT

Team 1: Human Neurogenetics

Name of the supervisor: Mr Laurent Villard

THEMES OF THE TEAM

Team 1 has focused its research projects on the following rare neurodevelopmental genetic disorders: Rett syndrome (RS), epileptic encephalopathies (EE) and, intellectual disability (ID). The team has a strong translational clinical research axis based on well-established collaborations with clinical centres at the local and national levels, particularly for EE thematic. The projects aim to identify new genetic causes and to characterise them based on cellular models (iPSC), to better understand phenotypic and genetic heterogeneity through the study of patients' cohorts, and to translate research results to preclinical studies and clinical trials. The team also has a research scientific focus on the development of models to characterise and better understand the physiopathology of disorders studied in the unit.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous Hcéres committee has recommended to the team
(i)' to make a major effort to publicise their research findings and achievements at a higher level.'
Over the period 2016-2021, the team has maintained an important and very regular activity of publications in good-quality journals but are not in high-ranking journals as underlined by the previous Hcéres committee. However, all the members of the team, PhD students included, published during this period.

(ii) 'to increase its participation in international networks (mainly European) and an effort to participate in H2020 and E-Rare projects should be done'
In its self-evaluation, Team 1 reports its participation to scientific boards of two European networks (RS Europe and European Joint project on rare diseases) during the previous period.
Two PIs of the team have obtained international fundings from private foundations and are co-partners of European projects (H2020, ANR) on RS and EE.

(iii) *'to make a major effort of active interaction with the environment, especially participation in patient associations.'* The committee considered '*involvement of team 1 in the social, economic and cultural environment is still poor*'.
During this period, several team members have been involved in national and European medical and/or scientific boards of associations. Team 1 was also actively engaged in public activities (public debates, patient's association, school training…)

WORKFORCE OF THE TEAM

Permanent personnel in active employment	
Professors and associate professors	1
Lecturer and associate lecturer	0
Senior scientist (Directeur de recherche, DR) and associate	2
Scientist (Chargé de recherche, CR) and associate	1
Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées)	0
Research supporting personnel (PAR)	3
Subtotal permanent personnel in active employment	**7**
Non-permanent teacher-researchers, researchers and associates	0
Non-permanent research supporting personnel (PAR)	1
Post-docs	1
PhD Students	5
Subtotal non-permanent personnel	**7**
Total	**14**

EVALUATION

Overall assessment of the team

The team has developed strong interactions with clinicians and has produced significant and innovative results based on its expertise on cellular and *in vivo* models. The publication record has been very good to excellent over this period. Its attractiveness and visibility are excellent. Several clinicians have recently joined this team and numerous collaborative research projects have been developed. The team has obtained highly competitive grants and several members have been invited to international meetings.
The socio-economic interactions are excellent to outstanding, notably with the obtention of contracts with pharmaceutical companies and dissemination activities for patient's associations.

Strengths and possibilities linked to the context

The strong point of this team is the scientific coherence of its research projects which are in adequacy with the available resources (patients' cohorts, phenotype databases, technological approaches) and the expertise of the team members in genomic studies, cellular and preclinical *in vivo* models as well as in clinical studies. As the assumed final and ultimate goal of the team is to develop new therapies in the area of rare, severe and orphan neurodevelopmental disorders, the development of a new Kcnq2 in vivo model and of trials they have already promoted or which are soon expected, represent strong indicators of projects progression and achievement. This coherence has resulted in a significant number of publications in high-quality scientific journals, invitations to present their results at international conferences and the obtaining of very competitive fundings.
Hence, from 2016 to 2021, the team has published 143 original papers including 45 scientific articles and 104 clinical research articles. Members of the team have published, as first, last or corresponding authors, 21 scientific articles and fourteen clinical research articles.
All the permanent researchers, postdoctoral scientists and, PhD students participated to the 49 scientific articles. The four clinicians related to this team have published both scientific and clinical articles. The team has also set up collaborations with other groups at national level and for rare genetic entities, at international level.
The attractivity of the team is very good and members are recognised at both national and international levels. Three members of the team have been regularly invited to international meetings (n=12). The team has obtained

highly competitive grants either as coordinator (3 ANR, 4 from private foundations and 2 from PACA region) or as partner (1 with NIH project, 2 in Europeans projects and 3 with AFM-Telethon).
Moreover, during this term, one CRCN mobility from another Inserm unit has joined the group in 2019 and reinforced the research axis on ID. Of note, another CRCN with a specific expertise in electrophysiology, will join the group for the next term. Finally, two clinicians (PH) have joined the team in 2018.
The team has filed an intellectual property declaration in the field of Kcnq2 epilepsy in 2021 and has established contracts for its knock-in Kcnq2 model with two pharmaceutical companies (Roche, Biogen).
The team widely shares its knowledge with the general public and participates in numerous events aimed at informing the public and families of affected patients

Weaknesses and risks linked to the context

The team currently has only one postdoctoral fellow, whereas the team has obtained significant funding since 2019 allowing it to recruit. The number of PhD students (3 over the period, 2 currently) is also limited in comparison with the number of researchers/EC who have their HDR in this team.

The ID research project does not yet have its own funding. This team has identified about ten genes that are potentially causative of ID and are currently in the process of publication and/or functional validation. The publication of these results should allow this team to obtain funding. It is also important that the researchers of this team obtain their HDR in order to recruit PhD students.

From a general point of view, there is no significant participation of the team in editorial boards of scientific journals.

RECOMMENDATIONS TO THE TEAM

The general impression is that the team, because of its clinical expertise, its access to cohorts of genotyped and clinically well-characterised patients, its well-established network of collaborations at the local and national level and on the other hand, with the tools developed (cellular and in vivo models) and the results obtained on MECP2 in the RS and on KCNQ2 in the EE, focuses all its research on these two projects giving a scientific coherence to its projects and leading to good level publications but not in high-ranking generalist journals. The team should make an effort to access these high impact journals.
As the team has recruited a permanent researcher in 2019 (and another one will join the team soon), it should start to diversify its projects and take more risks in its research projects in order to access high-impact journals.

Team 2: Ageing, prenylation & cancer

Name of the supervisor: Mr Nicolas Levy

THEMES OF THE TEAM

The team evaluates the role of ncRNAs in Hutchinson-Gilford syndrome (*HGPS*) and related progeroid syndromes. Further, several miRs such as miR-376a-3p and miR-376b-3p as well as miR-140-5p and miR-140-3p have been identified as actors of premature aging. In 2020, the team has discovered the MADaM syndrome where patients develop HGPS-like phenotypes. In 2018, the group 'Networks and Systems Biology for Diseases' was created (when one person moved from the Institute of Mathematics to the MMG) aimed at developing computational approaches to exploit 'omics' data. The team also works on spermatogenesis and human male infertility.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The main considerations of the former committee were to 1) increase the staff with permanent full-time researchers and more generally to reinforce its human resources; 2) to increase its attractivity. Overall, this has been achieved. During the last five years, the group has been reinforced by the arrival of one CNRS DR1 and two Inserm fellows. Further, the team has attracted several postdocs from foreign countries.
Concerning the organisation of the team, recommendations to increase junior members' skills was also followed.

WORKFORCE OF THE TEAM

Permanent personnel in active employment	
Professors and associate professors	8
Lecturer and associate lecturer	4
Senior scientist (Directeur de recherche, DR) and associate	4
Scientist (Chargé de recherche, CR) and associate	1
Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées)	0
Research supporting personnel (PAR)	8
Subtotal permanent personnel in active employment	**25**
Non-permanent teacher-researchers, researchers and associates	1
Non-permanent research supporting personnel (PAR)	5
Post-docs	2
PhD Students	15
Subtotal non-permanent personnel	**23**
Total	**48**

EVALUATION

Overall assessment of the team

The team is well recognised in its fields and made significant contributions. The publication record within the period is quantitatively excellent but most of them published in MDPI journals (except some of them in high-level journals). The team collaborates with numerous teams at the local area but also participates in several international networks, indicating a clear international visibility. The socio-economic interactions are excellent to outstanding, with a strong valorisation activity as well as remarkable clinical and societal interactions.

Strengths and possibilities linked to the context

The team is highly visible in the field of Hutchinson-Gilford syndrome (*HGPS*) and related progeroid syndromes. They made significant observations concerning ncRNA as well as miRNAs in progeroid syndromes and also discovered a HGPS-like syndrome named Madam syndrome. They also display a clear expertise on human infertility and spermatogenesis where they also made significant advances.
The was very productive during the period. It published several papers in high-level journals but also numerous ones in MDPI journals (Genes, Cells, Int. J. Mol. Sci. and Frontiers – F. Genetic, F. Physiol. F. Cell. Dev. Biol.]) that do not fall in the same category. All researchers published significantly during the period.
The team develops many collaborations within the Hopital la Timone itself but also at the level of Marseille University. They also belong to international networks and have developed numerous international collaborations. The team obtained considerable funding through competitive calls, including major grants from AFM, several ANR as coordinator or partner, and strong support from Amidex.
The team attractivity is also illustrated by the incorporation of three permanent researchers and recruitment of three foreign postdoc fellows. However, the recent and abrupt resignation of the team leader has been a matter of perturbation and reorganisation, the outcomes of which are pending. However, this can be seen with optimism since the new arrival is an important asset for the team that brings valuable new competences in the unit.

Non-academic links are excellent (AFM), scientific cooperation foundation (Fondation maladies rares) and with one private company (Progelife). The team has hosted a PhD student with a Cifre contract. Of importance, the team has obtained four patents and participated in the creation of two start-ups.
A few prizes have been obtained during the period that are either of local importance (Grand prix Départemental pour la Recherche en Provence) or more prestigious (Allianz).
Furthermore, the team has very tight links with patient's associations.

Weaknesses and risks linked to the context

Although the team welcomes three permanent researchers, the staff remains largely composed of MCU-PH, PU-PH etc… with clinical duties. These clinicians publish but the team should reinforce their potential with EPST researchers.
The publications are quantitatively excellent but the overall production suffers from numerous publications in medium level. The team should aim at enhancing its publication record qualitatively. The team does not host international researchers for middle-long stays.
The different sub-thematics of the team seem loosely connected.

RECOMMENDATIONS TO THE TEAM

The team should continue their nice work but should perhaps focus more on a given area since progeria and related syndromes and infertility and spermatogenesis appear relatively distant fields.
Further, the team should try to reach a better balance between clinicians and EPST researchers by trying to recruit additional permanent researchers.
Finally, the team should increase the qualitative level of its publications.

Team 3: Translational neuromyology

Name of the supervisor: Mr Marc Bartoli

THEMES OF THE TEAM

The main topic of the Team is focused on improving general knowledge in neuromuscular diseases for improving the care of patients with such rare orphan diseases. They perform both clinical and mechanistic studies in order to provide earlier and easier molecular diagnosis (significant activity in the discovery of new genes or new modes of transmission, strong link with routine diagnosis procedures at university hospital), to better appreciate the natural history of the diseases and their clinical phenotype variability, to decipher the biological pathways involved and finally to facilitate development of innovative specific disease-modifying treatments.
To this end, the team brings together a wide range of skills (clinics, genetics, cell biology, histology…) and tools (cells and *in vivo* models including zebrafish and murine)

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Recommendations of the previous report have been generally taken into account and addressed by the team leader. The new general organisation of this team and particularly the integration of one new arrival must be considered efficient and very successful six years later, according to the clear improvement of several inputs and of global quality of research. The involvement in platforms coordination constitutes also an important effort. The international visibility is still at a lower level than national reputation but international influence of the Team's clinicians is obvious. The attractiveness is high according to the origin of PhD students and postdocs.

WORKFORCE OF THE TEAM

Permanent personnel in active employment	
Professors and associate professors	2
Lecturer and associate lecturer	1
Senior scientist (Directeur de recherche, DR) and associate	2
Scientist (Chargé de recherche, CR) and associate	0
Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées)	0
Research supporting personnel (PAR)	4
Subtotal permanent personnel in active employment	**9**
Non-permanent teacher-researchers, researchers and associates	1
Non-permanent research supporting personnel (PAR)	0
Post-docs	1
PhD Students	10
Subtotal non-permanent personnel	**12**
Total	**21**

EVALUATION

Overall assessment of the team

This is clearly a team of clinician and geneticists with ambitious goals. Its scientific production is very good to excellent, they provided many new fundamental and clinical insights into the development and physiopathology of neuromuscular diseases. It is a very attractive team with a very good visibility both at the national and international level. Its socio-economic interactions are excellent, notably in term of outreach activities.

Strengths and possibilities linked to the context

The main strength of this team is the combination of excellent expertise's in clinical phenotyping of neuromuscular diseases as well as in genetics and in basic science. These combined expertise allow to propose excellent integrated science aimed to improve molecular diagnosis abilities, decipher physiopathological mechanisms and develop specific disease-modifying therapies.
Thanks to the high number of clinicians and geneticists among their members, the team has very strong skills to phenotype entities of interest and to improve quality and sensitivity of targeted next-generation sequencing as well was to develop exome/genome NGS use in such conditions. The team has contributed to the discovery of new genes or new modes of transmission involved in the diseases they are working on. Their privileged access to large-scale national and international cohorts ensures the feasibility of their projects focused on developing tools to improve the molecular diagnosis of neuromuscular diseases and to limit diagnostic wandering. The internal and external collaborations on this axis of research are fruitful as shown by the impressive level of collaborative publications. In addition, there are numerous methodological developments that are highly relevant to the clinic.
Understanding the mechanisms underlying the development of the diseases and development of specific treatment is another focus of the team, by the way claimed as their major focus. For this objective, the input of one PI is major as shown by the high level of publications and from fruitful international collaborations.
The leaders of the team have a solid national and international reputation in terms of expertise, and actively participate in medical and scientific councils in France. The team benefits from strong technical support (1 engineer and 3 half-time assistant-engineers) and is strongly implicated in development and coordination of platforms.
It obtained consequent funding, essentially through the AFM foundation or as partner on four ANR and one EU contract (FP7).
The scientific output of team's leaders is very good with 48 publications (24 in FLC position), mostly in strong speciality journals such as Annals of Neurology, Neurology, Journal of Neurology Neurosurgery and Psychiatry, American Journal of Human Genetics, Human Molecular Genetics and Journal Medical Genetics. Of note, the thesis work of students led to an average of 3.5 publications per student.
Link with non-academic partners have been supported through trials with clinicians of the team and with the development of a patented gene therapy to treat dysferlinopathies through the use of mini-gene expression, potentially usable in all affected patients whatever the mutation.
The team is extremely well connected with society. It has founded the mainstream annual event Recherch'thon and maintained it since> ten years. It is participating to ethical thoughts around the use of genetics and its societal consequences, and is particularly attentive to science dissemination among the youngest.

Weaknesses and risks linked to the context

The basic science research staff appears largely underrepresented compared to clinical and geneticists staff. This explains the unbalanced production between the highlighted priority topics of the team.

Internal collaborative projects with other MMG teams lead to publications in which last authors are generally from the other MMG teams.

RECOMMENDATIONS TO THE TEAM

The two research directors would need scientific reinforcement in order to achieve all the announced scientific objectives in such a large group of diseases like neuromuscular disorders.
The allocation of the technical staff among projects in progress/PIs may be clearly announced. Pathophysiological mechanisms studies need to be technically and scientifically more supported. Young basic scientists' recruitment needs to be encouraged to integrate the team to strengthen the fundamental lines of research and to favour the achievement of transversal translational projects.

According to the facilities for deep phenotyping, NGS analyses and access to large cohorts of patients, investigating the effects of gene modifiers or epigenetic mechanisms to explain phenotype severity variability may be a good additional goal in the future.

Team 4: Genetics & Development of Cardiac Defects

Name of the supervisor: Mr Stéphane Zaffran

THEMES OF THE TEAM

The team is interested in the cardiovascular system, mainly focusing on – but not restricted to - the outflow track and aortic valves. The team's projects aim to better understanding the cardiac development in order to get insights on the basis of Congenital Heart Diseases (CHD). Developmental studies combine in vivo and in vitro approaches to decipher the molecular mechanisms involved in cardiac cells specification and differentiation, identifying key transcription factors, mechanosensing channels or signalling pathways involved in cardiac cell fate. The relevance of the developmental findings in pathological context is explored taking advantage of different in vivo models and cohorts of patients. In parallel, analysis of cohorts and case reports allow the team to explore the genetic basis of CHD.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous report made some minor recommendations which have all been followed by the team.

'*The very good quality of the fundamental research produced by the team should be highlighted through publications in higher impact journals.*' The team has published 29 scientific articles and five reviews with major author positions, some of them in the most recognized journals, and clinical articles.

'*The expert committee recommends to apply for EU grants.*' One CRCN in the team, received EU funded fellowship (MSCA) and participated to one European Research Area Network on Cardiovascular (ERA-CVD). The PI participates to an international grant 2021-2024 (USA).

'*The expert committee recommends to keep records of the previous PhD students.*' All data obtained by the previous PhD students of the team are kept on both external hard disk and the data storage space of the unit.

'*The team should apply for ITN European grants*.' The team applied to an ITN European grant application (Succed) but scored below the funding threshold.

'*The AVM project should use the specific expertise of the team (iPSC, chicken model, …), to be competitive in the international scientific context.*' The PI who led the AVM project has recently joined another team. Therefore, the AVM project is no longer part of the team.

WORKFORCE OF THE TEAM

Permanent personnel in active employment	
Professors and associate professors	1
Lecturer and associate lecturer	2
Senior scientist (Directeur de recherche, DR) and associate	1
Scientist (Chargé de recherche, CR) and associate	1
Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées)	0
Research supporting personnel (PAR)	2
Subtotal permanent personnel in active employment	**7**
Non-permanent teacher-researchers, researchers and associates	0
Non-permanent research supporting personnel (PAR)	1
Post-docs	1
PhD Students	4
Subtotal non-permanent personnel	**6**
Total	**13**

EVALUATION

Overall assessment of the team

This is an excellent team, which has developed strong interactions with clinicians and has produced solid and innovative results concerning the mechanisms underlying cardiovascular development and diseases. The team's production is very good to excellent, notably through its collaborative projects. Its attractiveness and visibility are excellent, as illustrated by the recruitment of two postdocs who finally obtained permanent position, and by the success in competitive grants and invitations to international meetings. The team has excellent interactions with the society, especially through action towards young people.

Strengths and possibilities linked to the context

The team has a long-standing expertise in the field of cardiovascular development and disease, identifying key factors of cardiac cell specification and differentiation and genetic component of congenital heart diseases (CHD).

During the reporting period, the team developed new innovative projects, technical skills and tools. It deepened its knowledge on previously addressed scientific questions (Krox20 and aortic valves development and diseases; Hox genes in cardiac development and progenitors patterning; Congenital Melanocytic Nevi). In parallel, the team initiated a new project exploring mechanosensing of shear stress in valves development and pathologies and analysed CHD patients' exomes in search for genetic determinants of the pathologies. To address these projects, the team has developed new expertise (transcriptomic and Atacseq analysis) as well as new tools (an inducible Hoxb1 overexpressing *in vivo* model; a fluid activation device to apply controlled *in vivo*-like wall shear stress).

Team members have published, as first, last or corresponding authors, 29 scientific articles, five reviews and twelve clinical research articles in peer-reviewed journals, several of which in the best journals in the field. The team collaborates with other groups within the unit (25 co-publications with 5 MMG teams) and at both national and international levels (10 co-publications with collaborators in Spain, Tunisia, Germany, and with the Human

Cell Atlas project international consortium), leading to some very high-level publications. All the tenured researchers of the team participated to the 29 scientific articles. The two clinicians of the team also published both scientific and clinical articles. Thus, the production of the team is very good and its involvement in collaborative projects results in an excellent output.

The team visibility and attractivity are both excellent. Team members received numerous invitations to international meetings and symposia (e.g. American Heart Association – AHA – , Philadelphia 2019; Human Cell Atlas General Assembly meeting, Tokyo 2019; European Society of Cardiology, Newcastle 2016 and Vienna 2018; HCA Developmental and Pediatric Cell Atlas Meeting, Toronto 2021).
The group has obtained highly competitive grants: two European fundings (MSCA fellowship, ERA-CVD grant), five national grants (ANR, AORC, Inserm Prog Transversal), five charities and foundations grants (FFC, AFM-Téléthon, Multi-Fava) and two Lefoulon Delalande postdoctoral fellowships. The team leader participates to an international project funded by 'Single Ventricle Research Fund'. The team was coordinator/holder of six out of the twelve grants.
Importantly, during the reporting period, one researcher was recruited as CRCN Inserm (2016) and obtained an ANR-JCJC and another was awarded an ATIP-Avenir (2019).

The interactions of the team with the society are excellent: the team shares its knowledge with the general public, especially with young people, through yearly events (1000 chercheurs dans les écoles, Fête de la science) and by welcoming students from high school.

Weaknesses and risks linked to the context

Of the four permanent researchers that composed the team for the last few years, three recently have left the team, leaving the PI as the only permanent researcher of the team. This is the major concern for the future of the team.

While the team develops original projects and obtain strong results (highlighted in the Strength section), the journal where they are published do not always reflect their quality.

The team, which is internationally renowned, does not attract enough foreign postdoc.

RECOMMENDATIONS TO THE TEAM

The team needs to recruit new researchers (ideally with HDR to be able to supervise new PhD candidates) to strengthen the team. It should also hire postdocs, which should be feasible regarding its success to obtain a variety of competitive funding. Foreign postdocs and/or visiting professors would also increase the international visibility of the team.

Regarding the 2017 report, the team has increased the quality of the journals where it publishes its results, mainly in specialty journals (Cardiovascular, Development, Genetics). The team has the potential to further increase the proportion of articles published in the most recognized journals in the field and in generalist journals.

The team should help PhD student to submit publications as first author before defending their thesis (knowing that publishing high quality research articles can be difficult to achieve within the 3 years duration of thesis).

Team 5: Epigenetics, chromatin and disease Modeling

Name of the supervisor: Dr. Frédérique Magdinier

THEMES OF THE TEAM

Team 5 aims at understanding the influence of epigenetic mechanisms on determinism of human genetic diseases, essentially focused on facioscapulohumeral dystrophy (FSHD) but also on three different neurodevelopmental disorders.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

- *'The major recommendations from the previous Hcéres evaluation have been to enlarge the research project and to apply current epigenetic and cellular experimental capabilities to other genetic diseases. From the scientific point of view, the team should be more ambitious addressing the epigenetic and subtelomeric studies in other disorders that may share pathogenic mechanisms with FSHD'.*

A novel thematic related to non-canonical function of telomeres on genome-wide epigenetic regulation has been developed by a CRCN Inserm (from 2019; 3 publications).

- *'The unit should look into supporting the team leader further in providing iPSC expertise'.*

This recommendation was not addressed regarding the lack of technical support from Inserm or AMU to manage iPSC work and help coordinate MaSC core platform.

- *'The team should increase contacts and participation in international (mainly European) networks and projects, including H2020 and E-Rare.*

This recommendation was not addressed as they only obtained national grant (ANR, AID, doctoral fellowship) but the team leader became a member of the FSHD Europe Committee. In addition, the attractiveness of the team has considerably grown thanks to the recruitment of four international postdocs and participation in international conferences.

- *The number of postdoc researchers and PhD students should be increased. In this way it will be interesting to incorporate more international young researchers and students.*

The important growth of the team (previously considered as too small) with the arrival of three researchers including a permanent Inserm position obtained by an ex-post-doc while another postdoc is applying for a Junior Chair and Inserm position.

- *A major effort to maintain the translational pipeline and interactions among basic and clinical researchers and to increase active interactions with environment should be made, especially with patient associations.*

The team leader is the national referent of the FSH Research and Action Group of the AFM Telethon (Recherch'Thon, a local Telethon organisation, Mamara Institute), in charge of research on FSHD for the Neuromuscular Network (Filnemus). Two other team members are in charge of the diagnosis of the vast majority of patients affected with FSHD in France and part of the board of the national FSHD database.
Valorisation and patenting were considered with six patents over the past period, filed prior to publication or dissemination.

- *All PIs should participate in the supervision of PhD and master theses.*

Among the nine PhD thesis supervised during the period four of them were co-supervised with a member of the team.

WORKFORCE OF THE TEAM

Permanent personnel in active employment	
Professors and associate professors	1
Lecturer and associate lecturer	0
Senior scientist (Directeur de recherche, DR) and associate	1
Scientist (Chargé de recherche, CR) and associate	2
Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées)	0
Research supporting personnel (PAR)	1
Subtotal permanent personnel in active employment	**5**
Non-permanent teacher-researchers, researchers and associates	1
Non-permanent research supporting personnel (PAR)	0
Post-docs	3
PhD Students	8
Subtotal non-permanent personnel	**12**
Total	**17**

EVALUATION

Overall assessment of the team

The team develops an original line of investigation in a competitive field. It has produced excellent translational research on the role of epigenetics and chromatin conformation in rare diseases determinism. Its national visibility is excellent: it has strong links with geneticists and network on FSHD and it is involved in several medical and scientific councils at the national and international levels. It has been remarkably attractive for researchers and international post-doc and obtained substantial funding (2 AFM grants as collaborator and an Amidex emergence program). The socio-economic interactions are excellent to outstanding, notably through the improvement of diagnosis procedures for FSHD, obtention of industrial contracts, link with patient associations and dissemination activities.

Strengths and possibilities linked to the context

The team develops an original lines of research on a hot and competitive topic: the role of altered epigenetic regulation as a mechanism of human diseases determinism, in the two historical diseases of interest, FSHD1 and FSHD2, in the team. The investigations were extended to some developmental diseases (BAMS, Rubinstein Taybi syndrome…), in line with the recommendations of the previous Hcéres committee.
During this period, the team was remarkably attractive, as demonstrated by the arrival of three researchers including the recruitment of a young Inserm researcher following his postdoc in the lab. The team also supervised a very good number of PhD students (5) and postdoc (7) including four international fellows.
The level of fund raising is high, essentially through national grants (1ANR as coordinator and 4 as partner), charities (notably 2 important AFM grants as collaborator) and the local Amidex emergence program.
The team manages the biggest national cohort of FSHD through routine diagnostic procedures and has close link with the diagnostic lab and the national network of clinicians' expert of FSHD diseases. It has strong collaborations at international and national levels, including with the Translational Neuromyology team in the MMG.

The leaders of the team have a solid reputation in terms of expertise, and very actively participate in many medical and scientific councils in France. Their implications in creation and coordination of local platforms is excellent, with particularly valuable expertise for induced pluripotent stem cells culture and reprogramming.
The scientific output is very good to excellent according to the size of the team with 35 scientific articles including 21 as first or last author in high-level journals like Nucleic Acid research, J Med Genet, Pain, Circulation-genomic and precision medicine, Scientific report and Cells. International collaborations have led to publications in Nature Communication, PNAS, Stem Cells Translational Medicine … Sixteen reviews and nineteen clinical articles have also been published.

Its socio-economic interactions are remarkable: it produced new methodologies that are highly relevant to the clinic (6 patents filed during the last period), contributed to new recommendations for rare diseases treatment, participated in two clinical trials and developed several partnerships with industries for hiPSC production. The creation of two start-ups is debated and in progress with SATT Sud Est. Their participation in outreach activities and their link with patient association are also excellent.

Weaknesses and risks linked to the context

The recently recruited researchers need to take a stronger share in PhD supervision. PhD students are still essentially supervised by the team leader, even if an effort has been made to divide up tasks among young researchers.
In addition, with the absence of technical support, the team leader has too many responsibilities, notably with the direction of the unit and the MaSC core facility which is quite unique. It seems essential to provide some support to avoid a possible burn out of the team leader. The absence of a favourable answer from Inserm or AMU for this technical support requested since a long time is questionable for the committee.

According to its international visibility in epigenetics and FSHD, the level of international funding of the team should be increased, even in a highly competitive international context. The recent focus on developmental disorders may help to reach this goal but also represents a risk of dispersion.
A good portion of the strongest lead authors publications of the team are attributable to the activity of two researchers who arrived from another institute and work on a very different thematic. The synergy with the rest of the team and the longer-term benefit are not apparent.

RECOMMENDATIONS TO THE TEAM

The committee recommends that the PI obtain some technical support for the team/MaSC platform, and she should consider delegating some of her tasks and duties to other lab members. Obtaining technical support from Inserm or AMU administration to manage iPSC work of the unit and help to coordinate MaSC core platform is absolutely mandatory, especially as the team leader is also unit director.

A prioritisation of the several projects will be useful in the context of team members' expansion. A better synergy between the different researcher's projects should be sought. The initial historical focus of the team on FSHD1 an FSHD2 should be reinforced.

The efforts to publish its original works as lead author should be maintained.

Team 6: Bioinformatics and Genetics

Name of the supervisor: Mr Christophe Beroud

THEMES OF THE TEAM

In the reporting period, the team has developed locus-specific databases and bioinformatics tools for annotation and pathogenicity prediction of variants identified through high-throughput generation sequencing approaches. The team has also contributed to scientific projects of the others groups of MMG unit and external groups. The team mainly brought its bioinformatics expertise for the identification and characterisation of novel genes/variants and for the analysis of large datasets of phenotypic and molecular results of clinical cohorts.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The previous Hcéres committee has recommended to the team
(i) softwares be made available and released under an open-source licence and publication in methodology-focused journals. In the same vein, the committee has encouraged the team to optimize the team website
The team has now made available the software through a start-up company (GenOmnis) they created in 2017 with free access to academic researchers and also thanks to the development of a user-friendly website giving access to all tools developed by the team.

(ii) to increase its participation in international conferences and to attract foreign postdoctoral scientists.
Team members have given oral presentations at 30 international meetings in the reporting period. However, their communication remains limited with a sole methodological publication in NAR. This probably explains why this team is not sufficiently attractive for postdoctoral scientists (no recruitment since 2016).

(iii) the committee underlined 'The small size of the new team, with only two permanent scientists, presents another obvious risk'.
Since the departure of the oncogenetics group in 2017, it seems that the team has no more collaborations in the field of cancer. Moreover, the small size of the team explains its difficulties to remain competitive at the international level. In fact, NGS approaches has led to numerous and competitive developments of tools by large bioinformatics groups.

WORKFORCE OF THE TEAM

Permanent personnel in active employment	
Professors and associate professors	1
Lecturer and associate lecturer	1
Senior scientist (Directeur de recherche, DR) and associate	0
Scientist (Chargé de recherche, CR) and associate	1
Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées)	0
Research supporting personnel (PAR)	0
Subtotal permanent personnel in active employment	**3**
Non-permanent teacher-researchers, researchers and associates	0
Non-permanent research supporting personnel (PAR)	2
Post-docs	0
PhD Students	6
Subtotal non-permanent personnel	**8**
Total	**11**

EVALUATION

Overall assessment of the team

The presence of an expert team in bioinformatics is a strong point for this research unit which has several teams involved in the identification of new genes based on Omics approaches requiring the analysis and integration of data. The team has contributed to many publications but its own production could be strongly improved. The international integration of the team and its socio-economic interactions are very good. However, its attractivity and its size may hinder its capacity to remain competitive in this rapidly evolving field.

Strengths and possibilities linked to the context

The presence of a team expert in bioinformatics is an asset for the MMG unit, which has many scientific projects based on Omics approaches requiring bioinformatics analyses. This aspect is objectified by the numerous publications of MMG groups in which Team 6 is co-author. This is the main source of publications of Team 6, which also presented its contribution to various projects in more than 30 national and international conferences. They have also developed generic software to build and analyse locus-specific databases available to researchers implicated in rare disorders. The team has deposited their software/databases to the 'Agence pour la protection des programmes' and they made available their tools to the academic community through the team's web-site and the start-up they have created in 2017.
Besides, the team leader is holder of two national grants and participant of eight other projects including two European contracts (FP7, H2020). The valorisation potential of the team is well established, with one industrial partnership contract, one contract with the SATT Sud Est, and the creation of a start-up company. The team leader's reputation is also well attested: he serves as a communicating editor for Human Mutation and he is a board member of HGVS and Elixir hCNV community. The team also contributed to the organisation of scientific meetings (Jobim 2018, HGVS annual meetings…).

Weaknesses and risks linked to the context

Since the departure in 2017 of the Oncogenetics group, the team has collaborated with the other teams of the MMG unit but seems to have difficulties to develop its own scientific projects. In the reporting period, the team has published two methodological articles as first or last author in NAR and F1000 research. The team has one permanent researcher who has no paper as first, last or corresponding author.
The development of tools for annotation and interpretation of variants being a very competitive, dynamic and rapidly evolving scientific field, the limited size of the team is a risk to remain competitive in this field while national and international genomic platforms are organised themselves to meet this need.
This context partly explains the lack of major publications since 2019 and the difficulty for this team to be attractive for postdoctoral scientists. This issue also arises for the two PhD students recruited in 2018 and who will soon defend their PhD thesis. In addition one (productive) research engineer has recently left the team. The overall dynamic of the team is a major concern.

RECOMMENDATIONS TO THE TEAM

The team being small, in a very competitive international field of software developments, our recommendation is that it could serve as a transversal bioinformatics team responding to the specific needs of the MMG unit and offering its bioinformatics expertise to external scientific groups.
At the national level, the team could get closer to the genomic sequencing platforms and be a force for proposals for bioinformatics developments.

Team 7: Pathophysiology of cardiac development

Name of the supervisor: Mr Michel Pucéat

THEMES OF THE TEAM

The team develops fundamental research projects focusing on cardiac development, physiology and pathologies to identify new therapeutic targets for cardiovascular diseases.
Team members study the origin of cardiac malformations, the consequences of cardiac pathologies and the mechanisms underlying rare diseases affecting the heart by combining a wide range of technologies, from physiological measurements to omics and state-of-the art imaging. Through access to patient samples and the use/development of in vitro and in vivo models, they investigate the genetic, epigenetic and signalling pathways underlying the developmental/pathological processes they are interested in. In a strong translational effort, the team files patents based on its findings in cardiac regeneration and rare diseases.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

Most of the recommendations of the previous report have been followed.

'*The scientific production could be increased in number.*' The group published twelve manuscripts with major author position during the reporting period, compared to five during the previous period. It still needs to increase the number of research articles published.

'*The panel encourages team members to participate in more international meetings*.' The PI attended ten international conferences and the group members participated to six international meetings. Overall, team members gave 30 oral presentations, eleven of which were by students and postdocs, and team members were invited speakers in eleven meetings.

'*The expert committee recommends to keep records of the previous PhD students*.' The PI has given a complete record of former PhD students (publications and future).

'*The expert committee does not see any obvious weakness, except the team size*.' One group did not increase in size (in 2019, one permanent researcher left the team and a cardiac surgeon MCU-PH joined the team, no postdoc or permanent technical staff recruited). Another group, it has considerably increased in size since at the time of the visit it was composed of ten members, including two tenured researchers, two engineers, two postdocs and four PhD students.

WORKFORCE OF THE TEAM

Permanent personnel in active employment	
Professors and associate professors	0
Lecturer and associate lecturer	1
Senior scientist (Directeur de recherche, DR) and associate	1
Scientist (Chargé de recherche, CR) and associate	2
Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées)	0
Research supporting personnel (PAR)	1
Subtotal permanent personnel in active employment	**5**
Non-permanent teacher-researchers, researchers and associates	0
Non-permanent research supporting personnel (PAR)	0
Post-docs	1
PhD Students	8
Subtotal non-permanent personnel	**9**
Total	**14**

EVALUATION

Overall assessment of the team

The 2 groups which compose the team have both obtained highly interesting results on developmental and pathological mechanisms in human heart. The team has excellent to outstanding visibility and socio-economic interactions (4 patents filed, start-up interactions, strong involvement in civil society events). Its scientific production is very good with promising results for the junior group and excellent to outstanding for the senior group (36 peer-reviewed articles including 14 as major author mainly in high-level journals). Its attractiveness is excellent, with one clinician and one CR joining the team and being successful to obtain several competitive grants.

Strengths and possibilities linked to the context

The team is composed of two independent groups, who have separated their auto-evaluation.

first group
Despite its small size, this group had an excellent to outstanding scientific production: it characterised several mechanisms responsible for cardiac pathologies and rare diseases (e.g. atrial fibrillation, valves calcification, Cornelia de Lange Syndrome), and developed new in vitro models (e.g. hIPS cell model of valvulogenesis) and approaches (epigenetic) to study cardiac development and disease. These results gave rise to twelve publications with first, last or corresponding author from the group, most of which in the best journals of the field (Circ Res – 2 –, J Clin Invest, Sci Adv, Nat Comm). The group also published five reviews and eleven articles in collaboration (Nat Genet, Physiol Rev) and shares its knowledge beyond the usual range through reviews in French, protocol articles, and article written with social science colleagues about stem cell research.
The group shows a strong orientation toward valorisation as revealed by two patents filed or under process targeting rare diseases and regeneration of adult heart, and its close interaction with SATT and start-ups.
The international recognition and visibility of the group leader are excellent to outstanding as highlighted by several invitations to give talks in international conferences, such as Gordon Conference, by its involvement in many international research evaluation committees (in Europe, USA, Asia), its editorial activities (J Cardiovasc

Dev Dis), as well as national and international collaborations leading to high-level co-publications. The group leader is also member of a LIA (Ste Justine hospital, Montreal, Canada).
The group has obtained two international grants as holder (Leducq Foundation, one of which allowing the implementation of state-of-the-art imaging system), participated in two European grants (Europe IMI; Europe R-RARE) and is also funded by national foundations (FRM, Foundation de France), showing, together with the arrival of a cardiac surgeon, the excellent attractiveness of the group.
2nd group
This young group, which joined the team in late 2016 from IBDM, was initially composed of a CR researcher, a postdoc and a PhD student and has been strengthened by the arrival of a tenured researcher in 2019 and PhD students from 2018.
Its scientific production has been very good, with two research articles (Dev Dyn 2016, Cardiovasc Res ePub2021) as major authors that followed up on previous interests in cardiac development and diseases, and reviews from the team focusing on the role of FGF10 in the heart (Front Genet. 2018) and on the cardiomyocytes proliferation as a target for cardiac regeneration (Biochim Biophys Acta Mol Cell Res. 2020). They also published three articles in collaboration (Hum Mol Genet, eLife, Cells) and a MD-PhD student co-authored thirteen clinical publications. Utilizing a set of complementary technics (transcriptomics imaging, histology, molecular biology and biochemistry, primary culture) and developing its own material, such as a new genetic model, the team has identified novel molecular mechanisms involved in cardiac morphogenesis and unveiled novel therapeutic targets for heart regeneration.
The group has excellent to outstanding socio-economic interactions: strongly engaged in a valorisation and transfer effort, the group has patented a new therapeutic target and a second one is under the process of patenting. In parallel, all members are actively involved in events aimed at civil society (Fête de la science, Téléthon, high school debates, newspaper's interviews).
The visibility of the team is excellent: permanent researchers are members of editorial boards (Front Mol Med) and learned societies (SFC), they attended three international meetings as invited speakers and they are involved in evaluation committees for Inserm (CSS3), universities (AMU, Paris Saclay) and participate to the evaluation of scientific projects (ANR, ERC, FNS, FWF, MRC and ZonMW).
The group has been very successful to obtain competitive funding, holding three ANR grants and participating in a fourth one, as well as receiving grants and postdoctoral fellowships from foundations and associations (FFC, AFM-Téléthon). It must be noticed that three ANR and one AFM grants were obtained in 2021 (> 1.1 M€), securing funding until 2025. Thus, the team's attractiveness is also excellent, regarding the scientists who joined the lab and the success in grants applications.

Weaknesses and risks linked to the context

Both groups seem to have limited interactions with other teams of the unit.

No postdoc has been hired during 2016-2021, except the one that was at present at the creation of Rochais' group.

first group
Although the team received several highly funded grants during the reporting period (> 1 M€), the last one ended in 2020 and as of the end of 2021, no funds are secured for the next period.
A student, who defended her PhD in 2019 has not yet published research article as first author by the end of 2021.
The PI is the only permanent researcher of the team and does not benefit from the help of technical staff.
It might be surprising that the PI does not participate to more international conferences or editorial board regarding his scientific production and international recognition, but this is likely due to his other activities (valorisation, international research evaluation) and the lack of technical staff in the group.

2nd group
For the 2016-2021 period, the major weakness of the team is its low publication rate, as only two original research articles have been published as major author during that period (plus one in collaboration and 2 peer-reviewed reviews). It should be mentioned that in late 2022, the team published recent results in Circulation Research, a major journal in the cardiovascular field. Together with the recent success in obtaining competitive grants, it is likely that the team will improve its publication rate in the future.
The group leader recruited three PhD students in 2018 and 2019; while the former one had not yet defended her thesis (2020), meaning that three to four PhD, and possibly master students, are supervised by one researcher at the same time.

RECOMMENDATIONS TO THE TEAM

first group

The team should help PhD students to submit publications as first author before defending their thesis (knowing that publishing high quality research articles can be difficult to achieve within the three years duration of thesis).

The team should apply for new grants and develop collaborations within its department/unit.

2nd group

The team should improve its publication rate.

The team should be very attentive to the supervision of its PhD (and master) students especially in case of a high ratio student/HDR.

The team should hire postdocs to strengthen its task force, which might be feasible regarding the recent funding. Foreign postdoc or invited researchers would also benefit to the team.

Team 8: Differentiation and Proliferation of Neuroendocrine Tissues

Name of the supervisor: Mr Thierry Brue

THEMES OF THE TEAM

The DIP-NET (Differentiation and Proliferation of Neuroendocrine Tissues) team was created in 2017 by the fusion of Prof. Thierry Brue's group studying the role of transcription factors in pituitary physiopathology, and Prof. Anne Barlier's group studying signalling in neuroendocrine tumours. The team studies the effects of changes in signalling and transcriptional pathways mediating communication both within and between the diverse cell types of neuroendocrine organs, particularly the pituitary gland.

CONSIDERATION OF THE RECOMMENDATIONS OF THE PREVIOUS REPORT

The Hcéres committee had recommended to the team to increase the proportion of publications with senior and corresponding authors. The team has followed this recommendation by doubling its original scientific production from 40 to 80 primary research articles, 37 of which had a permanent staff member as first, last or corresponding author.
To increase the academic attractiveness of the team, the Hcéres committee had recommended that team members participate more in the boards of scientific journals. The team has been very active on this point since senior researchers are now on twelve editorial boards and fifteen academic societies.
Regarding the recommendation to participate and organise meetings, three team members have organised five international conferences since 2020, while six team members have given 26 invited talks at international conferences.
Finally, in response to the recommendation to recruit more international personnel, the team has hired a PhD student from Vietnam.
In conclusion, the team followed all the recommendations of the previous evaluation.

WORKFORCE OF THE TEAM

Permanent personnel in active employment	
Professors and associate professors	5
Lecturer and associate lecturer	5
Senior scientist (Directeur de recherche, DR) and associate	0
Scientist (Chargé de recherche, CR) and associate	1
Other scientists (Chercheurs des EPIC et autres organismes, fondations ou entreprises privées)	0
Research supporting personnel (PAR)	4
Subtotal permanent personnel in active employment	**14**
Non-permanent teacher-researchers, researchers and associates	2
Non-permanent research supporting personnel (PAR)	1
Post-docs	0
PhD Students	5
Subtotal non-permanent personnel	**8**
Total	**23**

EVALUATION

Overall assessment of the team

It is an excellent team that has been able to assemble a wide range of skills from basic research to clinical research. The scientific production is excellent, with 295 publications, including many clinical cases but also 43 publications in specialised journals in endocrinology.
The visibility of the team is excellent since its members organise and participate in numerous scientific meetings. The team is recognised as a referent centre for neuroendocrine diseases.
The attractiveness of the team is very good but the level of funding and the number of PhD students are not commensurate with the team's large size. Its socio-economic interactions are excellent to outstanding, with strong interactions with industries and patient associations.

Strengths and possibilities linked to the context

The scientific achievements are numerous and excellent but we can highlight among them the development of one of the rare cell models of differentiation of pituitary cells from human induced pluripotent stem cells (hiPSC).
The scientific production is excellent with 43 publications in recognised scientific journals in the field of endocrinology such as European Journal of Endocrinology, Endocrine-Related Cancer, Journal of Clinical Endocrinology and Metabolism. It is also worth mentioning some remarkable contributions in the most visible journals such as Nature or The Lancet Diabetes & Endocrinology through collaborations. Overall, the team published 295 papers collecting 3346 citations during the current evaluation period, which is outstanding. 50% of the publications include PhD students.
The excellent international visibility of the team is reflected first of all by the fact that 40% of its publications are the result of international collaborations, in addition to 25 invitations to international conferences.
The activity of the team beyond the academic world is excellent to outstanding with the establishment of three contracts with pharmaceutical companies and two clinical trials. The team has obtained a large number of contracts with the AFM (Association Française contre les Myopathies). The team is also supported by Gefluc (Association de Lutte contre le Cancer en Entreprise), by the ARTC Sud (association for research on intracerebral tumours), the Blackswan Foundation in Switzerland…
A major point is the strong involvement of the team in seventeen meetings with patient associations on the subjects of pituitary disorders, CMN (congenital melanocytic naevus) syndrome, Sturge-Weber syndrome and PIK3CA-related disorders.
Several members of the team are involved in academic committees such as CNU 44.01, Inserm CSS1, the national exam of medical students.

Weaknesses and risks linked to the context

The massive scientific production is certainly impressive but one can regret a little that some emblematic articles of the team are missing in major generalist journals to further increase the excellent visibility of the team.
The team produces or possesses valuable resources such as tumour, tissue and DNA samples but does not sufficiently use them in the form of patents or other means.
The team has only one permanent researcher, which limits the conduct of its most fundamental lines of research.
The team seems to have initiated few collaborations with the other teams of the MMG unit.

RECOMMENDATIONS TO THE TEAM

This excellent team should try to hire one or more permanent researchers, or obtain contracts that allow for more postdocs to be recruited, to strengthen the more fundamental lines of the projects and publish, from time to time, in more visible generalist journals. The development of the team's resources must be encouraged.

CONDUCT OF THE INTERVIEWS

Date

Start: 30 novembre 2022 à 8 h 30

End : 30 novembre 2022 à 18 h

Interview conducted: on-site or online

INTERVIEW SCHEDULE

Marseille Medical Genetics
(MMG)

Director: Frédérique Magdinier

Program of the Hcéres Interview

November 30, 2022
Marseille

Hcéres Scientific Officer
Marie José Stasia marie-jose.stasia@hceres.fr Tel : 33 (0)6 80 51 89 32

MMG – Wednesday 30 November, 2022

8:00 - 8:15 **Testing Zoom connections**
8:15 - 8:30 **Closed session Expert Committee (EC) – Scientific Officer (SO)**

Assessment of the Unit, Scientific Plenary session

8:30 - 8:45 **Presentation of the EC to the staff members by SO**

8:45 - 9:15 **Presentation of the unit by Frédérique Magdinier** (20 + 10 min discussion with the committee)
Attending: EC, SO, all the unit members

Presentation of the teams

9:15 - 9:45 **Team 1:** Human Neurogenetics (Laurent Villard)
(20 min presentation+ 5 min questions)
Attending: Team members, EC, SO, director of Unit
+5′ private discussion with the PI; attending: EC +SO

9:45- 10:20 **Team 2: Ageing, prenylation & cancer (Nicolas Levy)**
2.1: Premature aging syndromes and lipodystrophies involving prenylated proteins (Patrice Roll)
(10 min presentation + 5 min questions)
2.2: Systems Biomedicine (Anais Baudot)
(10 min presentation + 5 min questions)
Attending: Team members, EC, SO, director of Unit
+5′ private discussion with the PIs; attending: EC +SO

10:20 - 10:50 **Team 3: Translational neuromyology (Marc Bartoli)**
(20 min presentation+ 5 min questions)
Attending: Team members, EC, SO, director of Unit
+5′ private discussion with the PI; attending: EC +SO

Break 15 min

11:05-11h35 **Team 4: Genetics & Development of Cardiac Defects (Stéphane Zaffran)**
(20 min presentation+ 5 min questions)
Attending: Team members, EC, SO, director of Unit
+5′ private discussion with the PI; attending: EC +SO

11:35 – 12:05 **Team 5: Epigenetics, chromatin and disease Modeling (Frédérique Magdinier)**
(20 min presentation+ 5 min questions)
Attending: Team members, EC, SO, director of Unit
+5′ private discussion with the PI; attending: EC +SO

12:05 – 12H35 **Meeting of the EC and SO (closed hearing)**

12:35 – 1:30 p.m. **Lunch Break**

1:30 p.m. – 2 p.m. **Team 6: Bioinformatics and Genetics (Christophe Beroud)**
(20 min presentation+ 5 min questions)
Attending: Team members, EC, SO, director of Unit
+5′ private discussion with the PI; attending: EC +SO

2 p.m. - 2:35 p.m. **Team 7: Pathophysiology of cardiac development (Michel Pucéat)**
7.1: Cardiac development and regeneration (Francesca Rochais)
(10 min presentation + 5 min questions)
7.2: Pathophysiology of cardiac development (Michel Pucéat)
(10 min presentation + 5 min questions)
Attending: Team members, EC, SO, director of Unit
+5′ private discussion with the PIs; attending: EC +SO

2:35 p.m. – 3:05 p.m. **Team 8: Differentiation and Proliferation of Neuroendocrine Tissues (Thierry Brue)**
(20 min presentation+ 5 min questions)
Attending: Team members, EC, SO, director of Unit
+5′ private discussion with the PI; attending: EC +SO

Break 10 min

3:15 p.m. – 3:45 p.m. **Meeting with the representatives of Inserm and University**
Attending: expert committee, representatives of Institutions, SO

3:45 p.m. – 4:15 p.m. **#1: Technical and administrative personnel *(all the experts)***
Attending: Technicians, Engineers, Administrative staff, EC

Parallel meetings: (2 sub-committees)

4:15 p.m. – 4:45 p.m. **#2: Thesis students and postdocs**
Attending: PhD students and postdocs, EC1

4:15 p.m. – 4:45 p.m. **#3: Researchers and professors**
Attending: Researchers except group leaders, EC2

Break 15 min

5 p.m.-5:30 p.m. **Meeting of the Committee with the head of the unit.**
Attending: Unit Direction, expert committee, SO

5:30 p.m.-6:30 p.m. **Meeting of the Committee (closed hearing)**

PARTICULAR POINT TO BE MENTIONNED

No particular points to mention.

GENERAL OBSERVATIONS OF THE SUPERVISORS

Le Président de l'université

au

Département d'Évaluation de la recherche - Hcéres

Objet : Observations de l'unité relatives au rapport d'évaluation des experts Hcéres

N/Réf. : VPR/LS/AMS/CM – 23-07

Dossier suivi par : Cécile Merle
Tél : 04 13 94 95 90
cecile.merle@univ-amu.fr

Vos réf : DER-PUR230023310 - MMG - Centre de Génétique Médicale de Marseille (Marseille Medical Genetics)

Marseille, le lundi 21 août 2023

Madame, Monsieur,

Je fais suite au mail que vous nous avez adressé le 09/06/2023 dans lequel vous me communiquiez le rapport d'évaluation Hcéres de l'Unité MMG - Centre de Génétique Médicale de Marseille (Marseille Medical Genetics).

Comme demandé dans ledit mail, je vous fais part des observations de portée générale :

The research center director and team leaders do not wish to make any general observation regarding the overall evaluation of the unit

We would like to make the following observations regarding two teams:

Team 2: Ageing, prenylation and cancer, headed by Nicolas Lévy

1- Concerning the following remark in the "weaknesses and risks" part "Although the team welcomes three permanent researchers, the staff remains largely composed of MCU-PH, PUPH etc…with clinical duties. These clinicians publish but the team should reinforce their potential with EPST researchers."

We should mention that among the HU researchers, the hospital biologists (PU-PH, MCU-PH or PH) are strongly involved in team's projects. At least 3 of them are PIs of their own projects, lead a group, obtained research grants and regularly supervise Masters and PhD students. Some of them also have general responsibilities within the unit.

Team 7: Pathophysiology of cardiac development.
Research group headed by F. Rochais's group

1- Three to four PhD, and possibly master students, are supervised by one researcher at the same time.

Among the 4 PhD students recruited from 2017 to 2021, 2.5 are under the supervision of Francesca Rochais, Inserm researcher with HDR (L Bouchard 100%, C Porada 100%, E Pelcé 50%), and 1 is under the supervision of the second permanent researcher with HDR in the group, Magali Théveniau-Ruissy (M Ehrhard, 100%).

Teams 1; 3; 4; 5 and 8 do not wish to make any general observation

Les tutelles du MMG, Aix-Marseille Université et l'INSERM, n'ont pas d'autres observations à formuler.

Vous souhaitant bonne réception des présentes,

Je vous prie de croire, Madame, Monsieur, l'expression de mes respectueuses salutations.

Eric BERTON

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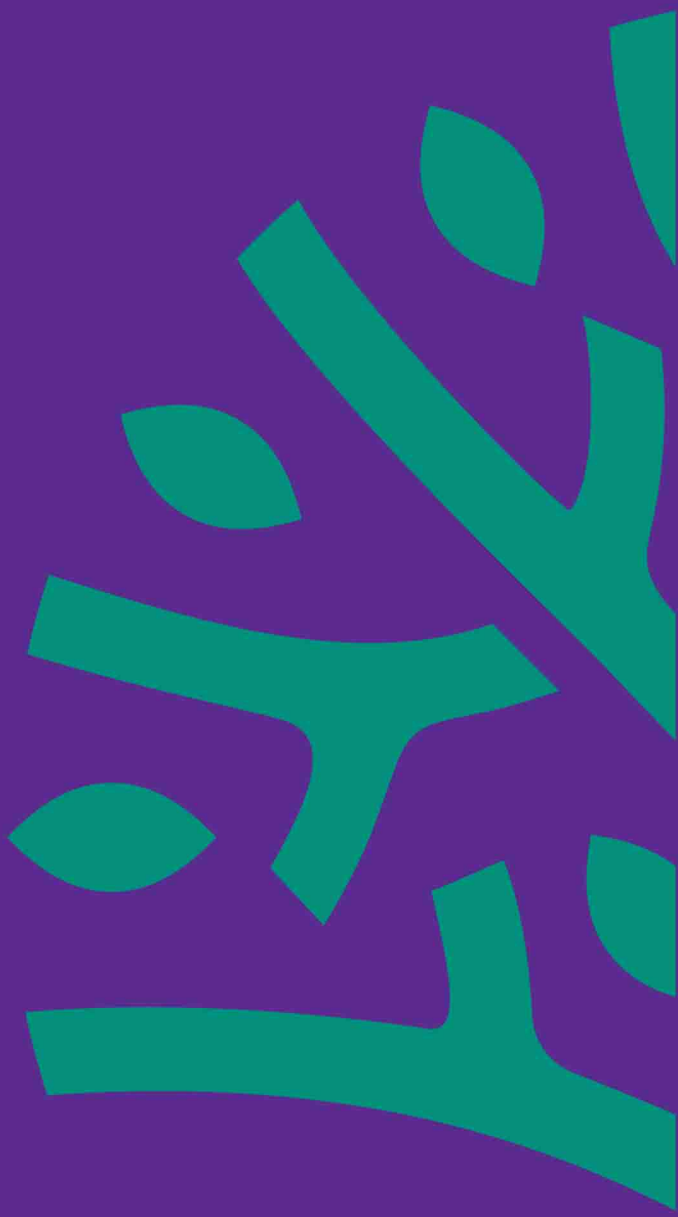

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